Regiospecificity of nucleophilic substitution in 4,6-dinitro-1-phenyl-1*H*-indazole

A. M. Starosotnikov, A. V. Lobach, V. V. Kachala, and S. A. Shevelev*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
47 Leninsky prosp., 119991 Moscow, Russian Federation.
Fax: +7 (095) 135 5328. E-mail: shevelev@mail.ioc.ac.ru

The reactions of 4,6-dinitro-1-phenyl-1*H*-indazole with anionic nucleophiles RS^- and N_3^- lead to the regiospecific replacement of the nitro group at position 4. The reaction with $N_2H_4 \cdot H_2O$ + $FeCl_3$ also results in reduction of only the 4-NO_2 group. Based on this fact, a procedure was developed for the preparation of previously unknown 3-unsubstituted 4-X-6-nitro-1-phenyl-1*H*-indazoles (X is a residue of a nucleophile or NH_2). Comparison of the data on the selective nucleophilic substitution (4-NO_2 group) in 3-Z-1-aryl-4,6-dinitro-1*H*-indazoles shows that in the case of Z = H, the regiospecificity of substitution is determined by the electronic effect of the annelated pyrazole ring.

Key words: 4,6-dinitro-1*H*-indazoles, nitro group, nucleophilic substitution.

Systematic studies on the nucleophilic substitution in the benzene fragment of 1*H*-indazoles, including the replacement of the nitro groups, are lacking in the literature. As part of continuing studies on the synthesis of benzoannelated heterocycles starting from 1-X-2,4,6-trinitrobenzenes, we have developed[1,2] a procedure for the preparation of 3-Z-1-aryl-4,6-dinitro-1*H*-indazoles (Z = CHO (**1**), CN (**2**), or 1,3-dioxolan-2-yl (**3**)) based on 2,4,6-trinitrotoluene (TNT). Under mild conditions, the reactions of 4,6-dinitroindazoles **1—3** with anionic N-, O-, and S-nucleophiles were found[1,2] to result in the regiospecific replacement of the nitro group at position 4, *i.e.*, at the position nearest to the heterocyclic moiety. High mobility of the 4-NO_2 group in 4,6-dinitroindazoles **1—3** may be associated with both the influence of the heterocyclic fragment (electronic effect) and rotation of the 4-NO_2 group out of the plane of the benzene ring under the influence of the 3-Z substituent in the *peri* position with respect to this group (steric effect).

Actually, the rotation of the nitro group can have a determining effect on the regiospecifity of the replacement of the nitro group with a nucleophile, as exemplified by the reactions of TNT.[3] The *p*-NO_2 group in the TNT molecule lies in the plane of the benzene ring, whereas both nitro groups in the *ortho* positions are substantially twisted out of the plane of the aromatic system due to the steric effect of the methyl group, and it is the *o*-NO_2 groups in TNT that are replaced in the reactions with the RS^- anions in spite of the fact that the steric and electronic (+I) effects of the Me group are unfavorable for the classical nucleophilic substitution. This phenomenon (steric complementarity) is attributable[3] to the fact that rotation of the aromatic nitro group relative to the ring facilitates the formation of the *ipso*-σ-complex. Quantum-chemical calculations (by different methods) of the structures of indazoles **1—3** demonstrated that the 6-NO_2 group in all compounds lies in the plane of the benzene fragment, whereas the 4-NO_2 group is rotated under the influence of the 3-Z substituent. The angle of rotation with respect to the plane of the aromatic ring depends on the character of the Z substituent. For example, the angles of rotation calculated by the AM1 method are 21.4° (Z = CHO), 42.5° (Z = 1,3-dioxolan-2-yl-), and 10.4° (Z = CN).

In this connection, it was of interest to study the direction and the ease of nucleophilic substitution in 3-unsubstituted 4,6-dinitro-1-phenyl-1*H*-indazole (Z = H), in which both the 6-NO_2 and 4-NO_2 groups are in the plane of the benzene fragment, and to compare these data with the results obtained for 3-substituted analogs, which could allow one to separate the electronic effect (Z = H) from the steric one.

4,6-Dinitro-1-phenyl-1*H*-indazole (**6**) was synthesized according to a known procedure[4,5] starting from 2,4,6-trinitrobenzaldehyde[6] (**4**) (Scheme 1).

Only data on the melting points of the target compound **6** and intermediate 2,4,6-trinitrobenzaldehyde *N*-phenylhydrazone (**5**) are available in the literature.[4,5] Earlier, these compounds have been identified only based on elemental analysis data, whereas their spectroscopic characteristics are lacking in the literature. We carried out a detailed study of the structure of dinitroindazole **6** using different spectroscopic methods and elemental analysis. In particular, we made the assignment of the signals of the

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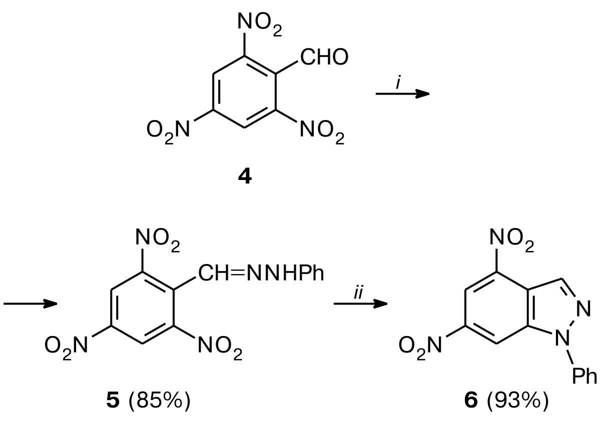
Scheme 1

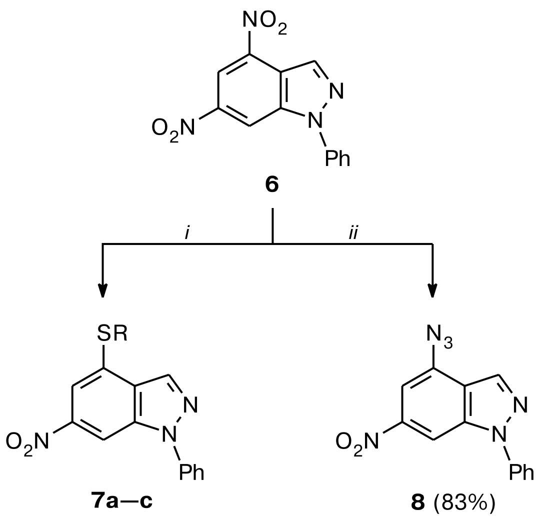


Reactions and conditions: *i*. $PhNHNH_2 \cdot HCl$, EtOH, 78 °C; *ii*. NaOH, H_2O/EtOH, 20 °C.

H and C atoms in the ^1H and ^{13}C NMR spectra of compound **6** based on the data on the complete assignment of the signals of the H and C atoms in mononitroindazole **7c** (see below).

We studied the reactions of indazole **6** with thiols as nucleophiles in the presence of K_2CO_3 or NaN_3 in *N*-methylpyrrolidone (NMP) or DMF. The reactions led to the replacement of the nitro group only at position 4 to give previously unknown 4-substituted 6-nitro-1-phenyl-1*H*-indazoles (Scheme 2).

Scheme 2



Reactions and conditions: *i*. RSH, K_2CO_3, NMP, 80—90 °C; *ii*. NaN_3, DMF, 80 °C.

Compound **7**	R	Yield (%)
a	Ph	57
b	4-Cl-C_6H_4	37
c	CH_2Ph	53

The reactions proceeded at 80—90 °C, *i.e.*, under more drastic conditions than those used in the reactions of 3-substituted dinitroindazoles **1** and **2** (20 °C).[2] This is, apparently, associated with their much higher electrophilicity compared to indazole **6** due to the presence of strong electron-withdrawing groups (CHO, CN) in compounds **1** and **2**. The nitro group at position 6 remained intact even in the presence of an excess of the nucleophile. Under more drastic conditions, the reactions led to destruction of the starting dinitroindazole **6**.

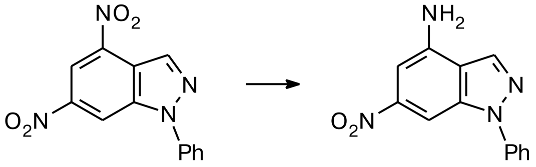
The fact that the reactions produced only one of two possible products of the replacement of the nitro group was established by ^1H NMR spectroscopy of the crude reaction product. The direction of substitution was proved as follows. We performed the complete assignment of the signals of the C and H atoms in the ^1H and ^{13}C NMR spectra of mononitro derivative **7c** based on the results of 2D ^1H-^{13}C NMR spectroscopy (HSQC, HMBC) and determined the chemical shifts of the C(4) (δ 133.5) and C(6) (δ 147.6) atoms. In the spectrum of the starting dinitroindazole **6**, the signal of the C(4) atom is observed at lower field (δ 138.7). The ^{13}C NMR spectra of other products of replacement of the nitro group, *viz*., mononitroindazoles **7a,b** and **8**, show signals of the C(4) atom at higher field (δ 132—135) compared to that in the spectrum of the starting dinitro derivative **6**, whereas the chemical shifts of the signals of the C(6) atom remain virtually unchanged (δ 147—148). These data provide unambiguous evidence that only the nitro group at position 4 is replaced regardless of the nature of the nucleophile used.

Judging from the times of conversion of the starting dinitroindazoles **1—3** and **6** performed under the same conditions with the use of benzylthiol as a nucleophile (*cf*. lit. data[1,2]), the rate of replacement of the nitro group in 3-unsubstituted dinitroindazole **6** is much lower than that in 3-formyl- and 3-cyanoindazoles **1** and **2** and is approximately equal to the rate of replacement of the 4-NO_2 group in dinitro derivative **3**.

Therefore, the regiospecific replacement of the 4-NO_2 group in dinitroindazole **6** is determined only by the electronic effect of the annelated pyrazole fragment. Apparently, this effect is not associated with the characteristic features of the electron density distribution in dinitroindazole **6**. Judging from the ^{13}C NMR spectroscopic data, the effective positive charge on the C(6) atom is even higher than that on the C(4) atom, because the signal of the C(6) atom is observed at much lower field than the signal of the C(4) atom (δ 145.4 and 138.7, respectively; the signals of the carbon atoms in the same aromatic system containing the same substituents are compared, *cf*. lit. data[7]). Apparently, the effect of the pyrazole ring consists in providing higher stability of the *ipso*-σ-complex of the nucleophile with dinitroindazole **6** at the C(4) atom compared to that at the C(6) atom.

Reduction of dinitroindazole **6** with hydrazine hydrate in the presence of iron(III) chloride afforded monoamino derivative **9** as the only reaction product, *i.e.*, the nitro group at position 4 was selectively reduced (Scheme 3).

Scheme 3



6 **9** (69%)

Reactions and conditions: $N_2H_4 \cdot H_2O$, C_{activ}, $FeCl_3 \cdot 6H_2O$, MeOH, 65 °C.

The fact that the reaction gave rise to the 4-amino derivative was confirmed by ^1H NMR spectroscopy. In particular, the NOESY experiment revealed the presence of interaction through space between the *ortho*-protons of the *N*-phenyl substituent and H(7) in compound **9** (δ 7.60). There are also interactions between the protons of the amino group and two other aromatic protons of the indazole system (H(5), δ 7.10; H(3), δ 8.65). These facts unambiguously confirm reduction of the nitro group at position 4.

Interestingly, the reactions with the use of other reducing systems (Fe/HCl—H_2O or Fe/CH_3COOH) also did not produce the isomeric 6-amino derivative. In all cases, only the 4-NO_2 group was reduced.

The structures and compositions of the compounds were established by ^1H and ^{13}C NMR and IR spectroscopy and confirmed by elemental analysis.

To summarize, we developed a procedure for the synthesis of previously unknown 4-R-6-nitro-1-phenyl-1*H*-indazoles starting from 4,6-dinitro-1-phenyl-1*H*-indazole based on high mobility of the 4-NO_2 group and the ease of its reduction.

Experimental

The ^1H and ^{13}C NMR spectra were recorded on Bruker AC-200 and Bruker AM-300 instruments, respectively. The chemical shifts (δ) are given relative to Me_4Si. All samples for NMR spectroscopy were prepared in a 1 : 1 DMSO-d_6/CCl_4 mixture. The IR spectra were measured on a Specord M-80 instrument in KBr pellets. The course of the reactions and the purities of the compounds synthesized were monitored by TLC on Silufol UV-254 plates. The reactions were carried out with the use of anhydrous DMF. All other solvents were not subjected to special dehydration.

2,4,6-Trinitrobenzaldehyde[6] (4).* Several crystals of I_2 were added to a suspension of 2,4,6-trinitrotoluene (10 g, 44 mmol) and *N*,*N*-dimethyl-*p*-nitrosoaniline (7 g, 47 mmol) in pyridine (15 mL). The reaction mixture was stirred at 20 °C for 24 h. The precipitate that formed was filtered off, washed with cold acetone (30 mL), and dried in air to prepare 2,4,6-trinitrobenzaldehyde 4-(dimethylamino)phenylimine in a yield of 11.15 g (70%). The product was used without additional purification. A suspension of 2,4,6-trinitrobenzaldehyde 4-(dimethylamino)phenylimine (10 g, 27 mmol) in concentrated HCl (80 mL) was stirred at 60 °C for 2 h. The precipitate that formed was filtered off, washed with water, and dried in air to prepare 2,4,6-trinitrobenzaldehyde (**4**) in a yield of 5.19 g (77%). M.p. 118—120 °C (*cf.* lit. data[6]: 119 °C). ^1H NMR, δ: 9.17 (s, 2 H, Pic); 10.57 (s, 1 H, CHO).

2,4,6-Trinitrobenzaldehyde *N*-phenylhydrazone (5). A suspension of 2,4,6-trinitrobenzaldehyde (4 g, 16.6 mmol) and $PhNHNH_2 \cdot HCl$ (2.4 g, 16.6 mmol) in EtOH (50 mL) was refluxed for 24 h. After cooling, the precipitate that formed was filtered off, washed with cold EtOH (10 mL), and dried in air to prepare compound **5** in a yield of 5.19 g (85%). M.p. 213 °C (*cf.* lit. data[4]: 202 °C). ^1H NMR, δ: 6.94 (m, 1 H, Ph); 7.03 and 7.28 (both m, 2 H each, Ph); 8.11 (s, 1 H, CH=N); 8.89 (s, 2 H, Pic); 11.63 (s, 1 H, NH).

4,6-Dinitro-1-phenyl-1*H*-indazole (6). A solution of NaOH (0.12 g, 3 mmol) in water (5 mL) was added to a suspension of hydrazone **5** (1.0 g, 3 mmol) in EtOH (25 mL). The reaction mixture was stirred at ~20 °C for 1 h. The precipitate that formed was filtered off and recrystallized from EtOH to prepare dinitroindazole **6** in a yield of 0.8 g (93%). M.p. 157—159 °C (EtOH) (*cf.* lit. data[5]: 148 °C). ^1H NMR, δ: 7.59 (m, 1 H, Ph); 7.71 and 7.86 (both m, 2 H each, Ph); 8.86, 8.93, and 8.96 (all s, 1 H each, H_{arom}). ^{13}C NMR, δ: 113.3 (C(7)); 113.8 (C(5)); 119.9 (C(3a)); 123.3 (CPh_o); 128.5 (CPh_p); 129.8 (CPh_m); 134.3 (C(3)); 137.7 (CPh_{ipso}); 138.7 (C(4)); 139.5 (C(7a)); 145.4 (C(6)). IR, ν/cm^{-1}: 1532, 1344 (NO_2). Found (%): C, 54.55; H, 2.82; N, 19.37. $C_{13}H_8N_4O_4$. Calculated (%): C, 54.93; H, 2.84; N, 19.71.

Synthesis of mononitroindazoles 7a—c (general procedure). A mixture of dinitroindazole **6** (0.28 g, 1 mmol), the corresponding thiol (1 mmol), and K_2CO_3 (0.14 g, 1 mmol) in NMP (5 mL) was stirred at 80—90 °C for 5 h. The reaction mixture was cooled, poured into water (50 mL), acidified to pH 2, and extracted with ethyl acetate (3×30 mL). The organic layer was dried over $MgSO_4$, the solvent was evaporated, and the residue was chromatographed on a column (SiO_2 35-63/toluene).

6-Nitro-1-phenyl-4-phenylthio-1*H*-indazole (7a). The yield was 57%. M.p. 128—130 °C. ^1H NMR, δ: 7.50—7.80 (m, 11 H, Ph, H(5)); 8.32 (s, 1 H, H(7)); 8.40 (s, 1 H, H(3)). ^{13}C NMR, δ: 105.1, 114.5, 122.8. 123.4, 126.5, 127.8, 129.2, 129.7, 129.9, 130.3, 132.6, 133.1, 134.0, 137.0, 138.4, 146.9. IR, ν/cm^{-1}: 1524, 1336 (NO_2). Found (%): C, 65.55; H, 3.89; S, 9.17. $C_{19}H_{13}N_3O_2S$. Calculated (%): C, 65.69; H, 3.77; S, 9.23.

4-(4-Chlorophenyl)thio-6-nitro-1-phenyl-1*H*-indazole (7b). The yield was 37%. M.p. 144—146 °C. ^1H NMR, δ: 7.28—7.75 (m, 10 H, H(5), Ph, 4-ClPh); 8.33 (s, 1 H, H(7)); 8.43 (s, 1 H, H(3)). ^{13}C NMR, δ: 105.7, 115.8, 122.8, 127.0, 127.8, 129.1, 129.6, 129.8, 130.0, 131.2, 134.0, 137.1, 138.4, 146.9. Found (%): C, 59.93; H, 3.28; S, 8.17. $C_{19}H_{12}ClN_3O_2S$. Calculated (%): C, 59.76; H, 3.17; S, 8.40.

4-Benzylthio-6-nitro-1-phenyl-1*H*-indazole (7c). The yield was 53%. M.p. 123—125 °C. ^1H NMR, δ: 4.51 (s, 2 H, CH_2); 7.26—7.86 (m, 10 H, Ph); 7.92 (s, 1 H, H(5)); 8.32 (s, 1 H,

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* Improved procedure.

H(7)); 8.42 (s, 1 H, H(3)). ^{13}C NMR, δ: 36.2 (CH_2); 104.9 (C(7)); 133.3 (C(5)); 123.5 (CPh_o); 126.8 (C(3a)); 128.0 (CBn_p); 128.5 (CPh_p); 129.1 (CBn_m); 129.5 (CBn_o); 130.5 (CPh_m); 133.5 (C(4)); 134.8 (C(3)); 136.7 (CBn_{ipso}); 137.2 (C(7a)); 139.0 (CPh_{ipso}); 147.6 (C(6)). Found (%): C, 66.72; H, 4.03; S, 8.70. $C_{20}H_{15}N_3O_2S$. Calculated (%): C, 66.46; H, 4.18; S, 8.87.

4-Azido-6-nitro-1-phenyl-1*H*-indazole (8). A suspension of dinitroindazole **6** (0.28 g, 1 mmol) and NaN_3 (0.1 g, 1.3 mmol) in anhydrous DMF (5 mL) was stirred at 70—80 °C for 6 h. After cooling, the reaction mixture was poured into water and acidified to pH 3. The precipitate that formed was filtered off and recrystallized from EtOH. The yield of compound **8** was 0.23 g (83%). M.p. 127—129 °C (EtOH). ^{1}H NMR, δ: 7.51 (m, 1 H, Ph); 7.66 (t, 2 H, Ph, ^3J = 6.0 Hz); 7.78 (m, 3 H, Ph, H(5)); 8.33 (s, 1 H, H(7)); 8.46 (s, 1 H, H(3)). ^{13}C NMR, δ: 103.4, 104.7, 120.7, 122.7, 127.8, 129.7, 132.8, 134.5, 137.9, 138.3, 147.2. IR, ν/cm^{-1}: 2128 (N_3); 1528, 1344 (NO_2). Found (%): C, 55.85; H, 2.49. $C_{13}H_8N_6O_2$. Calculated (%): C, 55.72; H, 2.88.

4-Amino-6-nitro-1-phenyl-1*H*-indazole (9). Ferric chloride hexahydrate (20 mg) and $N_2H_4 \cdot H_2O$ (0.2 mL, 8 mmol) were added to a suspension of dinitroindazole **6** (0.57 g, 2 mmol) and activated carbon (0.18 g) in MeOH (40 mL). The reaction mixture was refluxed for 1 h (TLC control). Then the hot mixture was filtered off from the carbon and the filtrate was cooled. The precipitate that formed was filtered off, washed with cold MeOH (10 mL), and dried in air. The yield of compound **9** was 0.35 g (69%). M.p. 142—144 °C. ^{1}H NMR, δ: 6.56 (s, 2 H, NH_2); 7.10 (s, 1 H, H(5)); 7.42 (t, 1 H, Ph, ^3J = 6.0 Hz); 7.60 (m, 3 H, H(7), Ph); 7.71 (d, 2 H, Ph, ^3J = 6.0 Hz); 8.53 (s, 1 H, H(3)). ^{13}C NMR, δ: 92.34 (C(7)); 96.5 (C(5)); 117.2 (C(3a)); 122.2 (CPh_o); 126.8 (CPh_p); 129.4 (CPh_m); 134.3 (C(3)); 138.3 (C(4)); 139.2 (CPh_{ipso}); 143.5 (C(7a)); 148.7 (C(6)). Found (%): C, 61.25; H, 4.09. $C_{13}H_{10}N_4O_2$. Calculated (%): C, 61.41; H, 3.96.

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