Functionalization of 4,6-dinitro-2-phenylindole at position 7

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Transformation of the amino group in 7-amino-1-methyl-4,6-dinitro-2-phenylindole afforded a number of new 7-R-4,6-dinitroindoles and a first representative of a novel tricyclic heteroaromatic system of [1,2,5]oxadiazolo[4,3-*g*]indole.

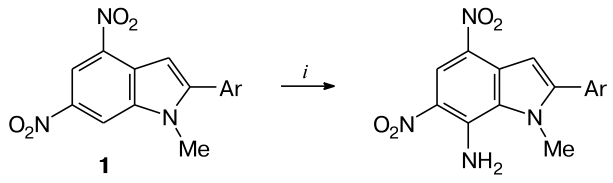
Key words: indoles, nitro compounds, amino group, diazotization, nucleophilic substitution.

The present work continues a series of investigations into the functionalization and annulation of indoles of a new type (2-aryl-4,6-dinitroindoles), which have become accessible *via* transformations of 2,4,6-trinitrotoluene.[1] Because indoles are very important as a basis for many biologically active natural and synthetic compounds with different spectra of action,[2] creation of indole systems with new combinations of substituents, as well as with annulated heterocycles, is of current interest.

Previously,[3] we functionalized 2-aryl-4,6-dinitroindoles at position 3 and obtained various 4-substituted 3-R-6-nitroindoles *via* regiospecific nucleophilic substitution of the 4-NO_2 group. Further transformations gave polycyclic *peri*-annulated systems.

The goal of the present work was to study functionalization of 2-aryl-1-methyl-4,6-dinitroindoles **1** at position 7. Earlier,[4] it was found that these compounds can be aminated at position 7 with 1,1,1-trimethylhydrazinium iodide (TMHI) in the presence of Bu^{t}OK under the conditions of vicarious nucleophilic substitution to give *ortho*-nitro amines **2** (Scheme 1). Transformation of the 7-NH_2 group would make it possible to use 2-aryl-4,6-dinitroindoles as a basis for the preparation of new indole derivatives with potentially useful biological activity.

Scheme 1

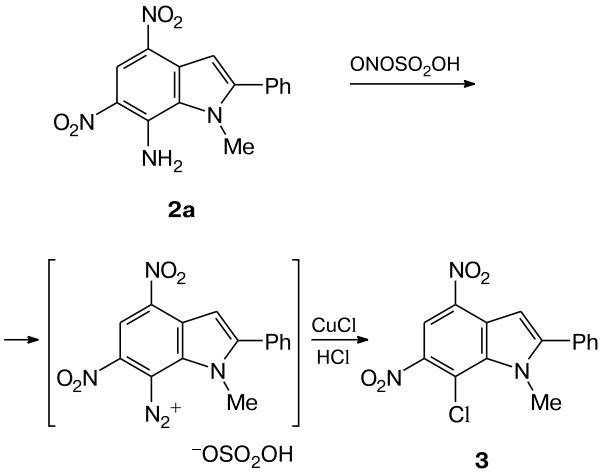


1 **2**

i. TMHI, Bu^{t}OK, DMSO, 20 °C.

We studied diazotization of amine **2a** (Ar = Ph) and found that nitrosylsulfuric acid should be employed as a nitrosating agent. Usually, this acid is used to obtain diazonium salts from weakly basic amines (*e.g.*, dinitroanilines[5]). Treatment of a solution of diazonium salt **2a**′ with a solution of cuprous chloride in HCl gave chloride **3** in 65% yield (Scheme 2).

Scheme 2



We studied reactions of chloride **3** with a number of S-, N-, and O-nucleophiles (Scheme 3). It turned out that chloride **3** reacts with NaN_3 in DMF even at room temperature to give azide **5** in high yield (see Scheme 3). A room-temperature reaction of chloride **3** with methyl thioglycolate in MeOH in the presence of Et_3N as a base afforded the corresponding sulfide **6**. More drastic conditions (60 °C) were required for a reaction with MeONa; the expected methoxy derivative **4** was obtained (see Scheme 3).

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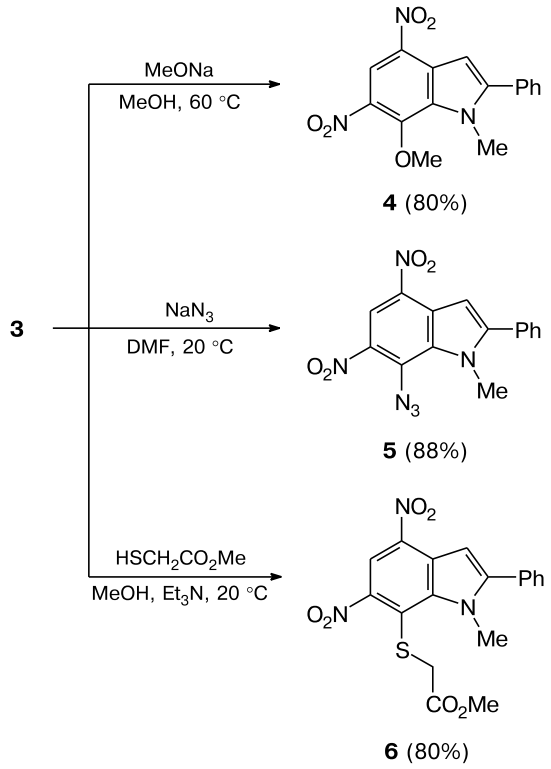
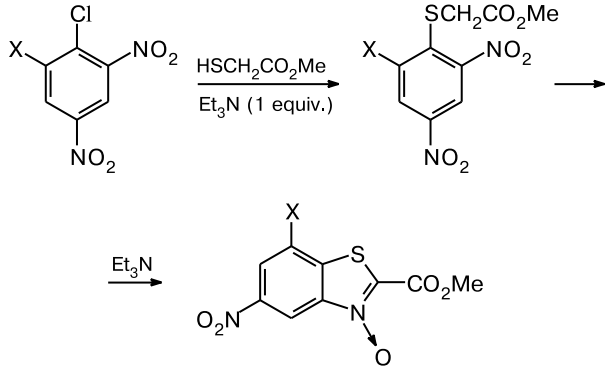
Scheme 3



Thus, chloride **3** is similar to 1-chloro-2,4-dinitrobenzene in reactivity and substitution rate.[6,7]

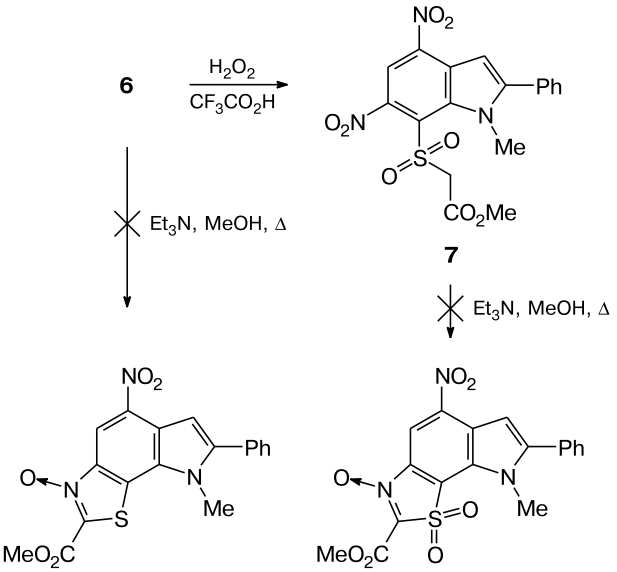
It is known[7] that an intermediate formed in reactions of 1-chloro-2,4-dinitro-6-X-benzenes (X = Me, NO_2, *etc.*) with methyl thioglycolate in the presence of a small excess of a base undergoes *in situ* cyclization into benzothiazole *N*-oxide through addition of an active methylene unit in the fragment SCH_2CO_2Me to the adjacent NO_2 group (Scheme 4).

Scheme 4



However, no cyclization product was obtained from sulfide **6** under the substitution reaction conditions even with an excess of Et_3N. In addition, attempted cyclization of sulfide **6** was unsuccessful (Scheme 5). To activate the methylene unit, we oxidized compound **6** into the corresponding sulfone **7**. Nevertheless, treatment of the latter with Et_3N in methanol at 60 °C yielded no cyclization product (see Scheme 5).

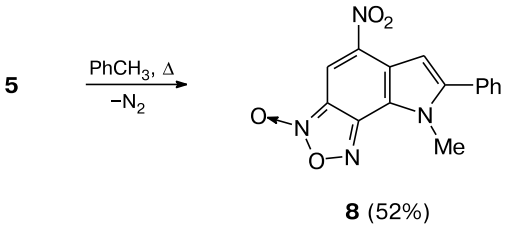
Scheme 5



Apparently, cyclization through an interaction of the active methylene unit with the 6-NO_2 group in sulfide **6** or sulfone **7** is hindered by the lowered electrophilicity of this group because of the strong π-abundant character of the pyrrole fragment of indole, which is largely transferred to the benzene ring.[8]

Reflux of azide **5** in toluene resulted in its intramolecular cyclization into furoxan derivative **8** (Scheme 6).

Scheme 6



Note that the literature data on the synthesis of indole derivatives containing an annulated furoxan ring are lacking. It should be emphasized that tricyclic compound **8** can be of interest for biological investigations because of a combination of indole[2] and furoxan fragments, which exhibit high and various biological activities. Furoxans serve as a source of exogenous nitrogen oxide, a versatile regulator of physiological processes.[9] Nitrobenzofur-

oxans inhibit metabolism in lymphocytes.[10] A known alternative route to furoxans *via* oxidation of *o*-nitroanilines[11] failed in our case: furoxanoindole **8** was not obtained from compound **2a** under the action of sodium hypochlorite or $PhI(OAc)_2$.

The structures of all compounds obtained were confirmed by NMR and IR spectroscopy (their IR spectra show characteristic absorption bands of the main functional groups: NO_2, NH_2, N_3, *etc.*), mass spectrometry, and elemental analysis.

To sum up, starting from 7-amino-4,6-dinitroindole derivatives, we synthesized a number of new 7-R-4,6-dinitroindoles and a first representative of a novel tricyclic heteroaromatic system of [1,2,5]oxadiazolo[4,3-*g*]indole.

Experimental

^{1}H NMR spectra were recorded on a Bruker AM-300 instrument in DMSO-d_6. Chemical shifts are referenced to Me_4Si. IR spectra were recorded on a Specord M-80 instrument (KBr pellets). Mass spectra were recorded on an MS-30 Kratos instrument (EI, 70 eV). The course of the reactions was monitored and the purity of the products was checked by TLC on Silufol UV-254 plates. Reactions were carried out in dry DMF and DMSO. The other solvents were not specially dried.

1-Methyl-4,6-dinitro-2-phenyl-1*H*-indole (1a). Potassium *tert*-butoxide (5.7 g, 51 mmol) was added to a solution of 4,6-dinitro-2-phenylindole[1] (4.7 g, 17 mmol) in DMF (60 mL). The mixture was stirred for 30 min. Then MeI (4.2 mL, 64 mmol) was added in portions at 30—35 °C. The reaction mixture was stirred at 25—30 °C for 2 h. The precipitate that formed was filtered off, washed with water, and dried in air to give compound **1a** (4.2 g, 85%), m.p. 227—229 °C (*cf.* Ref. 2: m.p. 222—224 °C). Found (%): C, 60.84; H, 3.62; N, 13.95. $C_{15}H_{11}N_3O_4$. Calculated (%): C, 60.61; H, 3.73; N, 14.14. ^{1}H NMR, δ: 4.01 (s, 3 H, Me); 7.31 (s, 1 H, H(3)); 7.57—7.84 (m, 5 H, Ph); 8.90 (s, 1 H, H(5)); 8.97 (s, 1 H, H(7)).

7-Amino-1-methyl-4,6-dinitro-2-phenyl-1*H*-indole (2a). Potassium *tert*-butoxide (4.5 g, 40 mmol) was added to a solution of indole **1a** (6.0 g, 20 mmol) and TMHI (8.0 g, 40 mmol) in DMSO (90 mL). The mixture was stirred at ~20 °C for 30 min, poured into ice water, and acidified. The precipitate that formed was filtered off, washed with CCl_4, and recrystallized from pyridine to give compound **2a** (5.5 g, 88%), m.p. >300 °C (*cf.* Ref. 2: m.p. >300 °C). Found (%): C, 57.37; H, 3.98; N, 17.73. $C_{15}H_{12}N_4O_4$. Calculated (%): C, 57.69; H, 3.87; N, 17.94. ^{1}H NMR, δ: 4.03 (s, 3 H, Me); 7.13 (s, 1 H, H(3)); 7.51—7.68 (m, 5 H, Ph); 8.21 (s, 2 H, NH_2); 8.79 (s, 1 H, H(5)). IR, ν/cm^{-1}: 3500, 3348, 1576, 1496, 1452, 1320, 1244, 1044, 964, 772, 728, 700.

7-Chloro-1-methyl-4,6-dinitro-2-phenyl-1*H*-indole (3). Amine **2a** (3.12 g, 10 mmol) was suspended in a mixture of AcOH and CF_3COOH (9 : 1) (100 mL). A solution of $NaNO_2$ (2.1 g, 20 mmol) in H_2SO_4 (20 mL) was added dropwise at 5—15 °C to the suspension. The resulting solution of the diazonium salt was stirred for 30 min at the above temperature and poured at 0 °C into a solution of CuCl (9.0 g, 60 mmol) in HCl (70 mL). The mixture was stirred for 2 h, left in a refrigerator for ~14 h, and then poured into ice water. The precipitate that formed was filtered off, washed with water, and dried in air to give compound **3** (2.2 g, 65%), m.p. 195—200 °C. Found (%): C, 54.62; H, 3.31; Cl, 11.24; N, 12.13. $C_{15}H_{10}ClN_3O_4$. Calculated (%): C, 54.31; H, 3.04; Cl, 10.69; N, 12.67. ^{1}H NMR, δ: 4.12 (s, 3 H, Me); 7.30 (s, 1 H, H(3)); 7.55—7.79 (m, 5 H, Ph); 8.65 (s, 1 H, H(5)). IR, ν/cm^{-1}: 1612, 1560, 1516, 1484, 1464, 1344, 1300, 1272, 1172, 1148, 992, 892, 816, 768, 720, 700. MS, *m/z*: 331 $[M]^+$.

7-Methoxy-1-methyl-4,6-dinitro-2-phenyl-1*H*-indole (4). Sodium methoxide (0.11 g, 2 mmol) was added to a solution of chloride **3** (0.33 g, 1 mmol) in MeOH (15 mL). The reaction mixture was stirred at 60 °C for 3 h, cooled, and poured into acidified water. The precipitate that formed was filtered off, washed with water, and dried in air to give compound **4** (0.26 g, 80%), m.p. 173—176 °C. Found (%): C, 58.49; H, 4.12; N, 13.01. $C_{16}H_{13}N_3O_5$. Calculated (%): C, 58.72; H, 4.00; N, 12.84. ^{1}H NMR, δ: 4.03 (s, 3 H, Me); 4.15 (s, 3 H, OMe); 7.25 (s, 1 H, H(3)); 7.55—7.80 (m, 5 H, Ph); 8.70 (s, 1 H, H(5)).

7-Azido-1-methyl-4,6-dinitro-2-phenyl-1*H*-indole (5). Sodium azide (0.25 g, 3.9 mmol) was added to a solution of chloride **3** (0.44 g, 1.3 mmol) in DMF (7 mL). The reaction mixture was stirred at 20 °C for 24 h. The precipitate that formed was filtered off, washed with water, and dried in air to give compound **5** (0.4 g, 88%), m.p. 158—160 °C. Found (%): C, 53.03; H, 2.58; N, 24.43. $C_{15}H_{10}N_6O_4$. Calculated (%): C, 53.26; H, 2.98; N, 24.84. ^{1}H NMR, δ: 4.12 (s, 3 H, Me); 7.27 (s, 1 H, H(3)); 7.55—7.80 (m, 5 H, Ph); 8.79 (s, 1 H, H(5)). IR, ν/cm^{-1}: 2152, 1604, 1576, 1520, 1508, 1472, 1444, 1352, 1332, 1312, 1168, 1148, 1016, 904, 896, 824, 768, 756, 724, 696.

Methyl 2-[(1-methyl-4,6-dinitro-2-phenyl-1*H*-indol-7-yl)thio]acetate (6). A mixture of chloride **3** (0.33 g, 1 mmol), methyl thioglycolate (0.18 mL, 2 mmol), and Et_3N (0.3 mL, 2.2 mmol) in MeOH (30 mL) was stirred at ~20 °C for 24 h. Then the solution was poured into acidified water. The precipitate that formed was filtered off, washed with water, and dried in air to give compound **6** (0.32 g, 80%), m.p. 127—130 °C. Found (%): C, 53.64; H, 3.93; N, 10.61; S, 7.80. $C_{18}H_{15}N_3O_6S$. Calculated (%): C, 53.86; H, 3.77; N, 10.47; S, 7.99. ^{1}H NMR, δ: 3.95 (s, 3 H, Me); 4.10 (s, 2 H, CH_2); 4.15 (s, 3 H, Me); 7.25 (s, 1 H, H(3)); 7.37—7.75 (m, 5 H, Ph); 9.06 (s, 1 H, H(5)).

Methyl 2-[(1-methyl-4,6-dinitro-2-phenyl-1*H*-indol-7-yl)sulfonyl]acetate (7). A 30% solution of H_2O_2 (1.0 mL) was added dropwise to a solution of sulfide **6** (0.3 g) in trifluoroacetic acid (10 mL). The mixture was stirred at 20 °C for 1 h and poured into water (50 mL). The precipitate that formed was filtered off, washed with water, and dried in air to give compound **7** (0.28 g, 77%), m.p. 119—121 °C. Found (%): C, 50.07; H, 3.22; N, 9.54; S, 7.59. $C_{18}H_{15}N_3O_8S$. Calculated (%): C, 49.88; H, 3.49; N, 9.70; S, 7.40. ^{1}H NMR, δ: 3.49 (s, 3 H, Me); 4.60 (s, 2 H, CH_2); 4.15 (s, 3 H, Me); 7.37 (s, 1 H, H(3)); 7.57—7.85 (m, 5 H, Ph); 8.60 (s, 1 H, H(5)).

8-Methyl-5-nitro-7-phenyl-8*H*-[1,2,5]oxadiazolo[3,4-*g*]indole 3-oxide (8). A solution of azide **5** (0.395 g, 1.2 mmol) in toluene (20 mL) was refluxed for 12 h. The major part of the solvent was removed and the residue was diluted with hexane. The precipitate that formed was filtered off and dried in air to give compound **8** (0.19 g, 52%), m.p. 169—172 °C. Found (%): C, 57.95; H, 3.31; N, 18.17. $C_{15}H_{10}N_4O_4$. Calculated (%): C, 58.07; H, 3.25; N, 18.06. ^{1}H NMR, δ: 4.13 (s, 3 H, Me); 7.18 (s, 1 H, H(6)); 7.51—7.61 (m, 3 H, Ph); 7.65—7.71 (d, 2 H, Ph, ^3J = 8.2 Hz); 8.12 (s, 1 H, H(4)). IR, ν/cm^{-1}: 3096, 1612, 1580, 1540, 1516, 1484, 1456, 1436, 1392, 1332, 1192, 1052, 1036, 1020, 1008, 932, 848, 824, 808, 772, 716, 664.

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