TRANSFORMATIONS OF 2-ARYL-4,6-DINITROINDOLES

Vladimir V. Rozhkov,*[§] Alexander M. Kuvshinov, Svyatoslav A. Shevelev.

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky Prosp., 47, 117913, Moscow, Russia

Abstract: Some transformations of 2-aryl-4,6-dinitroindoles were studied. These indoles undergo *N*-methylation, formylation and can be regioselectively aminated with trimethylhydrazinium iodide. Upon reduction of *N*-methylated 2-aryl-4,6-dinitroindoles the corresponding diamines are obtained in good yields.

Introduction

Indoles containing nitro groups on the benzene ring are valuable precursors to some biologically active compounds.[1] Previously, we described a general method for the preparation of 2-aryl-4,6-dinitroindoles **1** starting from 2,4,6-trinitrotoluene.[2] An important feature of indoles **1** is the presence of two nitro groups at 4,6-positions of the benzene ring. Such a configuration opens new possibilities for functionalization of the benzene ring by vicarious nucleophilic substitution. At the same time the nitro groups could decrease the nucleophilicity of the heterocyclic ring. The purpose of this work was to investigate the reactivity of indoles **1** as well as to synthesize new derivatives.

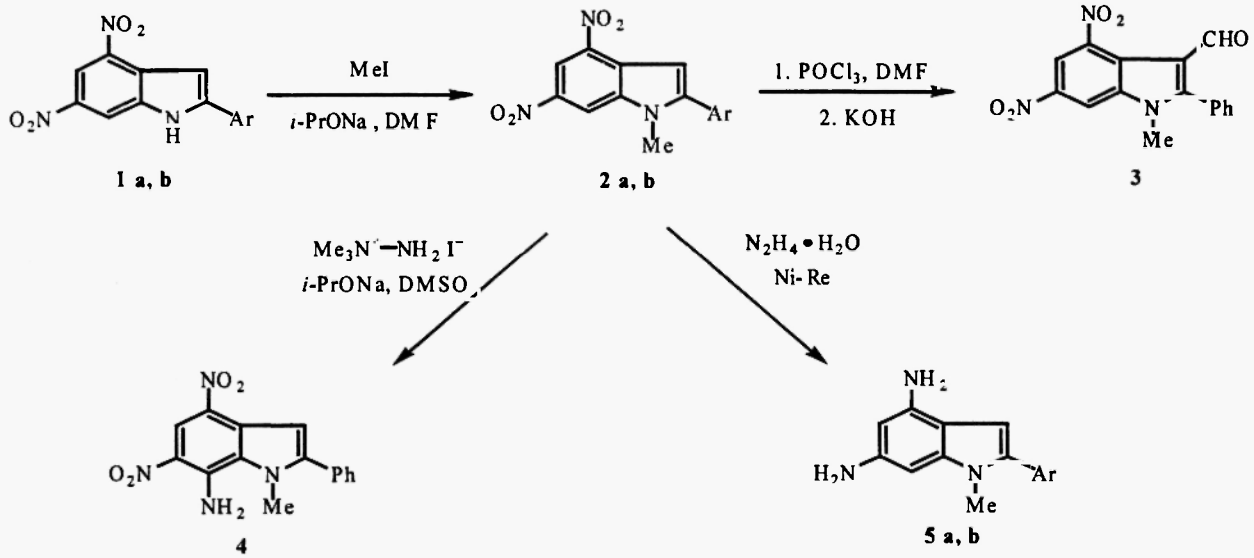
Results and Discussion

We have found that despite the presence of two strong electron withdrawing (EW) groups on the benzene ring, dinitroindoles **1** react with electrophilic reagents. Compounds **1** easily undergo *N*-methylation by reaction with MeI in the presence of *i*-PrONa (Scheme 1). The use of $(CH_3O)_2SO_2$ as the methylating agent resulted in lower yields of *N*-methylindoles **2**.

N-Methyldinitroindoles **2** undergo Vilsmeier-Haak formylation. This was shown using indole **2a** as an example. The 3-formylindole **3** was obtained in high yield; however, more rigorous

[§] Present address: *Department of Biochemistry and Biophysics, School of Medicine, University of Pennsylvania Philadelphia, PA 19104; USA, Fax: +1 (215) 573 3787; E-mail: rozhkov@mail.med.upenn.edu*

conditions were necessary (excess $POCl_3$, 60-70 °C) compared with indoles free of EW substituents.[3] On the other hand, the presence of two electron withdrawing *meta* nitro groups increases the reactivity of **2** toward nucleophiles. For example, *N*-methylated dinitroindole **2a** can be aminated at the benzene ring with trimethylhydrazinium iodide by way of the Vicarious Nucleophilic Substitution (VNS).[4] Trimethylhydrazinium iodide has been previously employed for ring amination of some nitrobenzenes.[5] The important feature of our amination reaction is that it occurs regioselectively and yields only a single product. The selectivity of the process was confirmed by NOESY analysis of the resulting novel aminodinitroindole **4**. The spin-spin interactions were observed only between -NH_2 and N-Me protons, which unambiguously proves that the substitution occurs exlusively at the 7-position.



Scheme 1

It was also found that *N*-methylated indoles **2** can be conveniently reduced to the corresponding diaminoindoles **5**. These aminoindoles are quite stable in the solid state and can be stored in air with no visible decomposition. On the contrary, their solutions are unstable in the presence of air at room temperature.

All attempts to reduce nitro groups in the *N*-unsubstituted dinitroindole **1** were unsuccessful. A complex mixture of products was obtained.

Experimental

Melting points were measured using a Boetius apparatus and are uncorrected. All reactions were monitored by TLC using Silufol (UV-254) precoated aluminiun plates. ^{1}H NMR spectra were recorded on a Brüker AC 200 spectrometer in DMSO-d_6 solution. Chemical shifts are reported in ppm downfield from TMS. Organic solvents and reagents were purified by standard literature procedures. Satisfactory microanalyses were obtained for all new compounds.

Synthesis of Methylated Dinitroindoles 2. Dinitroindole **1** (1 mmol) and *i*-PrONa (3 mmol) were stirred in DMF (20 mL) at rt for 1 h. Mel was added dropwise to the mixture, and the solution was stirred for 3 h at rt and then for 1 h at 80 °C. The mixture was poured into cold water (100 mL), acidified with HCl, and the resulting precipitate was crystallized from pyridine.

1-Methyl-4,6-dinitro-2-phenylindole (2a): Yield 92 %; mp 222-224 °C; ^{1}H NMR δ 3.86 (s, 3 H), 7.30 (s, 1H), 7.71 (m, 3 H), 7.90 (m, 2H), 8.78 (d, 1 H, J = 2.1 Hz), 8.91 (d, 1 H, J = 2.1 Hz).

2-(*p*-Diethylaminophenyl)-1-methyl-4,6-dinitroindole (2b): Yield 94 %; mp 221-223 °C; ^{1}H NMR δ 1.13 (t, 6 H, J = 7.1 Hz), 3.37 (q, 4 H, J = 7.1 Hz), 3.98 (s, 3 H), 6.82 (m, 2 H), 7.18 (s, 1 H), 7.56 (m, 2 H), 8.76 (d, 1 H, J = 2.1 Hz), 8.79 (d, 1 H, J = 2.1 Hz).

3-Formyl-1-methyl-4,6-dinitro-2-phenylindole (3). Dinitroindole **2a** (1.5 g, 1.7 mmol) was added to mixture of anhydrous DMF (20 mL) and $POCl_3$ (2.6 g, 17 mmol) and the solution was stirred at 70-75 °C for 5 h. The mixture was poured on ice (100 g) and treated with 10 mL of 65% HNO_3. The precipitate was dried, added to 200 mL of 10 % KOH, and the mixture was heated under reflux for 1 h. The resulting solution was filtered while hot, cooled, and acidified with HCl. Yellow crystals were collected by filtration and crystallized from pyridine; yield 85%; mp 225-228 °C; ^{1}H NMR δ 3.86 (s, 3 H), 7.69 (m, 5 H), 8.60 (d, 1 H, J = 2.2 Hz), 9.03 (d, 1 H, J = 2.2 Hz), 9.59 (s, 1 H).

7-Amino-1-methyl-4,6-dinitro-2-phenylindole (4). *i*-PrONa (4.9 mmol) was added to a solution of dinitroindole **2** (1.6 mmol) and trimethylhydrazinium iodide (4.9 mmol) in anhydrous DMSO (15 mL). The mixture was stirred for 3 h at rt and then poured into 75 mL of acidified

water. The precipitated solid was crystallized from pyridine; yield 93 %; mp >300 °C; ^{1}H NMR δ 4.02 (s, 3 H), 7.11 (s, 1 H), 7.69 (m, 5 H), 8.21 (br, 2 H), 8.79 (s, 1 H).

Reduction of *N*-Methyldinitroindoles 2. Hydrazine hydrate (6 mmol) and Ni-Re (50 mg) were added to a suspension of dinitroindole **2** (1mmol) in *i*-PrOH (20 mL) under Ar. The mixture was stirred for 3h at 50 °C and then heated under reflux for an additional hour. The solution was filtered while hot under Ar, cooled, and the precipitated solid was collected by filtration and dried under reduced pressure.

4,6-Diamino-1-methyl-2-phenylindole (5a): Yield 85 %; mp 134-136 °C; ^{1}H NMR δ 3.50 (s, 3 H), 4.59 (br, 2 H), 5.01 (br, 2 H), 5.67 (d, 1 H, J = 0.7 Hz), 5.84 (dd, 1 H, J = 2.1 and 0.7 Hz), 6.47 (d, 1 H, J = 2.1 Hz), 7.29-7.46 (m, 5 H).

4,6-Diamino-2-(*p*-diethylaminophenyl)-1-methylindole (5b): Yield 72 %; mp 94-96 °C; ^{1}H NMR δ 1.12 (t, 6 H, J = 7.1 Hz), 3.32 (q, 4 H, J = 7.1 Hz), 3.45 (s, 3 H), 4.50 (br, 2 H), 4.38 (br, 2 H), 5.65 (d, 1 H, J = 0.7 Hz), 5.82 (dd, 1 H, J = 2.1 and 0.7 Hz), 6.25 (d, 1 H, J = 2.1 Hz), 6.70 (m, 2 H), 7.24 (m, 2 H).

Acknowledgement. We thank the International Science and Technology Center (Project # 419) for financial support.

References

(1) A. R. Katritzky, S. Rachwal and S. Bayyuk, Org. Prep. Proced. Int. **23**, 357 (1991)

(2) V. V. Rozhkov, A. M. Kuvshinov, V. I. Gulevskaya, I. I. Chervin and S. A. Shevelev, Synthesis 2065 (1999)

(3) E. H. P. Young, J. Chem. Soc. 3493 (1958)

(4) M. Mąkosza and K. Wojciechowski, Acc. Chem. Res. **20**, 282 (1987); M. Makosza and K. Wojciechowski, Liebigs Ann. Chem. 1805 (1997)

(5) P. F. Pagoria, A. R. Mitchell and R. D. Schmidt, J. Org. Chem. **61**, 2934 (1996)

Received on November 8, 2000