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Amination of 1,3-Dihalo-2-nitrosobenzenes

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Abstract—1,3-Dichloro-2-nitrosobenzene and 1,3-dibromo-5-fluoro-2-nitrosobenzene reacted with amines to give previously unknown nitrosobenzene derivatives containing alkylamino groups in positions *3* and *5*.

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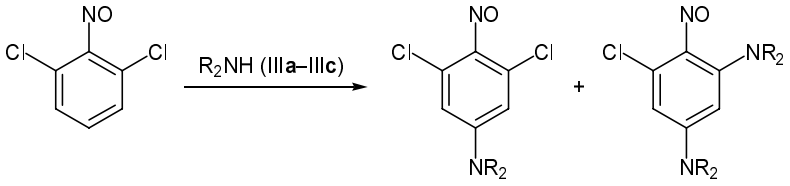
Nitroso group is a strong electron-acceptor substituent which activates arene derivatives toward aromatic nucleophilic substitution reactions. For example, 4-nitrosoaniline and its *N*-alkyl derivatives undergo transamination even in boiling diethyl ether [1], and they are converted into 4-nitrosophenol on heating in aqueous alkali [2]. As concerns nucleophilic replacement of a halogen atom in the *ortho* position with respect to the nitroso group, Boulton et al. [3] were the only to report that treatment of 1,3-dichloro-2-nitrosobenzene with sodium azide on heating leads to the formation of 4-chlorobenzofurazan, i.e. the reaction involves nucleophilic replacement of the chlorine atom by azide ion, followed by heterocyclization with participation of the azido and nitroso groups. There are no published data on nucleophilic substitution of the halogen atom in halonitrosoarenes by amines. On the other hand, nitrosobenzene and its analogs are known to react with aliphatic amines at the nitroso group to give products of redox processes, while their reactions with aromatic amines result in the formation of the corresponding azo compounds [4].

The presence of a nitroso and alkylamino groups in the *ortho* position with respect to each other, e.g., in the naphthalene series, gives rise to cyclization leading to naphthimidazoles [5]. More extensive use of *o*-nitrosoalkyl(aryl)aminoarenes in such heterocyclization is limited due to the absence of convenient methods for their preparation. Taking into account the above stated, the goal of the present work was to find synthetic routes to 1-nitroso-2,4-dialkylaminobenzenes starting from accessible polyhalonitrosoarenes.

We have found that 1,3-dichloro-2-nitrosobenzene (**I**) and 1,3-dibromo-5-fluoro-2-nitrosobenzene (**II**) readily react with cyclic amines and that compounds **I** and **II** behave differently in these reactions. Chromatographic monitoring of the reaction of compound **I** with morpholine (**IIIa**) in DMF at 0–5°C showed that the primary amination product is 4-(3,5-dichloro-4-nitrosophenyl)morpholine (**IVa**) (Scheme 1). However, monoamination product **IVa** reacts with the second amine molecule via nucleophilic replacement of the chlorine atom. As a result, diamination product **Va** is formed. Nucleophilic substitution of hydrogen and chlorine occurs at comparable rates; therefore, compound **IVa** cannot be isolated in a high yield. Moreover, 1,3-dichloro-2-nitrosobenzene is sparingly soluble in DMF and other organic solvents at low temperature, so that the transformation of **I** into **IVa** cannot be fast. Raising the temperature favors side

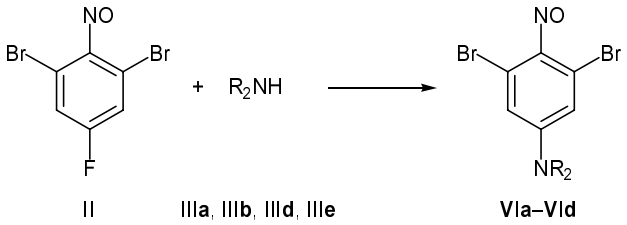
Scheme 1.



I IVa, IVb Va, Vc

R_2N = morpholino (**a**), pyrrolidin-1-yl (**b**), 4-phenylpiperazin-1-yl (**c**).

Scheme 2.



II IIIa, IIIb, IIId, IIIe VIa–VId

III, R_2N = piperidino (**d**), 4-cyclohexylpiperazin-1-yl (**e**); **VI**, R_2N = morpholino (**a**), pyrrolidin-1-yl (**b**), piperidino (**c**), 4-cyclohexylpiperazin-1-yl (**d**).

redox processes; therefore, the reaction cannot be performed at elevated temperature.

The reactions of compound **II** with amines result in nucleophilic substitution only of the fluorine atom (Scheme 2). One of the remaining halogen atoms can also be replaced using DMF as solvent. We thus succeeded in obtaining previously unknown nitroso compounds **VII** and **VIII** having two different amino groups at the aromatic ring (Scheme 3).

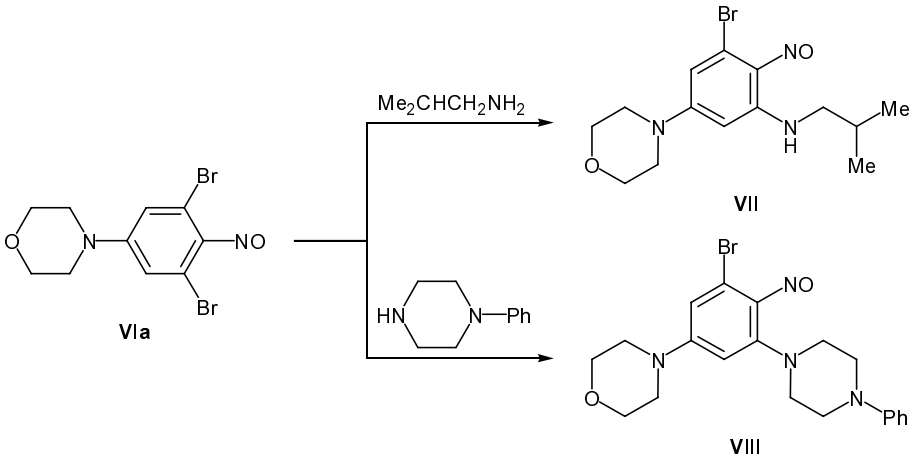
The structure of the isolated products was confirmed by spectral methods. Their electronic spectra contained absorption maxima at λ 380–420 (charge-transfer band in the aminoarene system) and 670–790 nm ($n\rightarrow\pi^*$ transition in the nitroso group); the spectra are typical of the simplest representatives of the nitrosobenzene series [6]. The spectral parameters of 2,6-dibromo-4-fluoronitrosobenzene (**II**) were consistent with its structure. Like other nitrosohaloarenes, compound **II** showed in the mass spectrum a triplet signal from the molecular ion $[M]^+$ with *m*/*z* 282–284, a triplet with *m*/*z* 252–254, a doublet with *m*/*z* 173–174, and ion peaks with *m*/*z* 93 and 74. The presence of the $[M - 30]^+$ ion peak is typical of aromatic C-nitroso compounds; this ion is formed by elimination of NO from the molecular ion [7]. Its subsequent fragmentation is likely to include successive elimination of bromine and fluorine atoms. The UV spectrum of **II** is analogous to those of known nitrosobenzene derivatives; the positions of absorption maxima and molar absorption coefficients (ε) almost coincide with the corresponding parameters of 1,3-dibromo-5-chloro- and 1,3,5-tribromo-2-nitrosobenzenes [8].

Thus the results of our study have confirmed the activating effect of nitroso group in aromatic nucleophilic substitution reactions, and a procedure for the synthesis of a new group of diaminonitrosoarenes has been developed.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker DRX-500 spectrometer (500 MHz) from solutions in DMSO-d_6 and $CDCl_3$ using tetramethylsilane as internal reference. The ^{1}H NMR spectrum of compound **II** (monomeric form) was recorded at 60°C, and of the other compounds, at 20°C. The electronic absorption spectra were measured on a Helios Epsilon spectrophotometer from solutions in toluene with concentrations of 0.5×10^{-4} (λ 325–600 nm) and 0.5×10^{-2} M

Scheme 3.



(λ 600–1100 nm) using 1-cm cells. The progress of reactions was monitored, and the purity of products was checked, by TLC on Silufol UV-254 plates. The melting points were determined on a Boetius melting point apparatus. The mass spectrum of 1,3-dibromo-5-fluoro-2-nitrosobenzene (**II**) was obtained on a Finnigan MAT 8200 instrument.

1,3-Dichloro-2-nitrosobenzene (**I**) was synthesized according to the procedure described in [9].

1,3-Dibromo-5-fluoro-2-nitrosobenzene (II). Acetic anhydride, 12 ml, was added under stirring at 0–5°C to a mixture of 5.38 g (20 mmol) of 2,6-dibromo-4-fluoroaniline, 28 ml of acetic acid, and 20 ml of 30% hydrogen peroxide, and the mixture was stirred for 48 h at 25°C. The precipitate was filtered off and purified by steam distillation, followed by recrystallization from acetic acid. Yield 3.30 g (58%), mp 100–101°C. UV spectrum, λ_{max}, nm (log ε): 340 (3.47), 775 (1.62). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.48 d (2H, J = 8 Hz). Found, %: C 25.52; H 0.32; N 4.91. $C_6H_2Br_2FNO$. Calculated, %: C 25.44; H 0.70; N 4.91.

4-(3,5-Dichloro-4-nitrosophenyl)morpholine (IVa). Morpholine, 0.87 g (10 mmol), was added over a period of 5 min to a mixture of 0.88 g (5 mmol) of 1,3-dichloro-2-nitrosobenzene in 10 ml of DMF under stirring at 0–5°C, and the mixture was stirred for 40 min at that temperature. The mixture was poured onto ice, and the green solid was filtered off, dried, and recrystallized twice from ethanol–benzene, 5:1. Yield 0.64 g (23%), mp 198–199°C. UV spectrum, λ_{max}, nm (log ε): 400 (4.22), 785 (1.81). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.62 t and 3.72 t (8H, CH_2), 7.08 s (2H, H_{arom}). Found, %: C 46.20; H 3.83; N 10.55. $C_{10}H_{10}Cl_2N_2O_2$. Calculated, %: C 45.97; H 3.83; N 10.72.

4,4'-(5-Chloro-4-nitroso-1,3-phenylene)dimorpholine (Va). Morpholine, 1.74 g (20 mmol), was added over a period of 5 min to a mixture of 1.76 g (10 mmol) of 1,3-dichloro-2-nitrosobenzene in 10 ml of DMF under stirring at 0–5°C, and the mixture was stirred for 60–90 min at that temperature. The mixture was poured onto ice, and the green solid was filtered off, dried, and recrystallized from ethanol. Yield 1.36 g (43%), mp 138–139°C. UV spectrum, λ_{max}, nm (log ε): 385 (4.27), 765 (2.18). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.90 t, 3.45 t, 3.84 t, and 4.02 t (4H each, CH_2); 5.86 d and 6.78 d (1H each, H_{arom}, J = 2 Hz). Found, %: C 53.68; H 6.05; N 13.22. $C_{14}H_{18}ClN_3O_3$. Calculated, %: C 53.93; H 5.77; N 13.48.

1-(3,5-Dichloro-4-nitrosophenyl)pyrrolidine (IVb). Pyrrolidine, 1.77 g (25 mmol), was added over a period of 5 min to a mixture of 1.76 g (10 mmol) of 1,3-dichloro-2-nitrosobenzene in 20 ml of DMF under stirring at 0–5°C, and the mixture was stirred for 40 min at that temperature. The yellow solid was filtered off, dried, and recrystallized from ethanol. Yield 0.63 g (26%), mp 191–192°C. UV spectrum, λ_{max}, nm (log ε): 410 (4.42), 785 (1.87). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.01 m and 3.50 m (8H, CH_2), 6.75 s (2H, H_{arom}). Found, %: C 48.42; H 4.15; N 11.25. $C_{10}H_{10}Cl_2N_2O$. Calculated, %: C 48.97; H 4.08; N 11.42.

1,1'-(5-Chloro-4-nitroso-1,3-phenylene)bis(4-phenylpiperazine) (Vc). *N*-Phenylpiperazine, 1.62 g (10 mmol), was added over a period of 10 min to a mixture of 0.88 g (5 mmol) of 1,3-dichloro-2-nitrosobenzene in 10 ml of DMF under stirring at 0–5°C, and the mixture was stirred for 5 h at that temperature. The green solid was filtered off, dried, and recrystallized from ethanol. Yield 1.05 g (45%), mp 168–169°C. UV spectrum, λ_{max}, nm (log ε): 390 (4.36), 765 (2.22). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 6.14 d and 7.04 d (1H each, 2-H, 6-H, J = 2 Hz); 6.82 m, 7.01 m, and 7.26 m (10H, H_{arom}); 3.10 t, 3.35 t, 3.45 t, and 3.75 t (4H each, CH_2). Found, %: C 67.16; H 6.64; N 15.08. $C_{26}H_{28}ClN_5O$. Calculated, %: C 67.60; H 6.06; N 15.16.

4-(3,5-Dibromo-4-nitrosophenyl)morpholine (VIa). Morpholine, 3.48 g (40 mmol), was added at 0–5°C to a suspension of 5.73 g (20 mmol) of 1,3-dibromo-5-fluoro-2-nitrosobenzene in 40 ml of ethanol, and the mixture was stirred for 50 min at that temperature. The yellow–green solid was filtered off, dried, and recrystallized from ethanol–benzene (5:1). Yield 6.75 g (95%), mp 186–187°C. UV spectrum, λ_{max}, nm (log ε): 405 (4.30), 790 (1.82). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.01 s (2H, H_{arom}), 3.46 t and 3.84 t (4H each, CH_2). Found, %: C 34.23; H 2.19; N 7.83. $C_{10}H_{10}Br_2N_2O_2$. Calculated, %: C 34.28; H 2.85; N 8.00.

1-(3,5-Dibromo-4-nitrosophenyl)pyrrolidine (VIb).) Pyrrolidine, 0.17 g (25 mmol), was added at 0–5°C to a suspension of 0.283 g (1 mmol) of 1,3-dibromo-5-fluoro-2-nitrosobenzene in 5 ml of ethanol, and the mixture was stirred for 10 min at that temperature. The yellow solid was filtered off, dried, and recrystallized from ethanol. Yield 0.28 g (85%), mp 200–210°C. UV spectrum, λ_{max}, nm (log ε): 420 (4.46), 780 (1.92). ^{1}H NMR spectrum ($CDCl_3$), δ,

ppm: 6.76 s (2H, H_{arom}), 2.08 m and 3.43 m (4H each, CH_2). Found, %: C 35.94; H 2.86; N 8.33. $C_{10}H_{10}Br_2N_2O$. Calculated, %: C 35.92; H 2.99; N 8.38.

1-(3,5-Dibromo-4-nitrosophenyl)piperidine (VIc). Piperidine, 0.17 g (2 mmol), was added at 0–5°C to a suspension of 0.283 g (1 mmol) of 1,3-dibromo-5-fluoro-2-nitrosobenzene in 5 ml of ethanol, and the mixture was stirred for 30 min at that temperature. The yellow solid was filtered off, dried, and recrystallized from ethanol. Yield 0.23 g (66%), mp 175–177°C. UV spectrum, λ_{max}, nm (logε): 415 (4.36), 785 (1.85). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.70 m and 3.50 m (10H, CH_2), 7.0 s (2H, H_{arom}). Found, %: C 37.69; H 3.18; N 7.82. $C_{11}H_{12}Br_2N_2O$. Calculated, %: C 37.93; H 3.46; N 8.0.

1-Cyclohexyl-4-(3,5-dibromo-4-nitrosophenyl)-piperazine (VId). *N*-Cyclohexylpiperazine, 0.33 g (2 mmol), was added at 0–5°C to a suspension of 0.283 g (1 mmol) of 1,3-dibromo-5-fluoro-2-nitrosobenzene in 5 ml of ethanol, and the mixture was stirred for 30 min at that temperature. The yellow solid was filtered off, dried, and recrystallized from toluene. Yield 0.35 g (81%), mp 134–135°C (from toluene). UV spectrum, λ_{max}, nm (logε): 415 (4.36), 785 (1.90). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 6.98 s (2H, H_{arom}), 2.34 m (1H, CH), 2.71 t and 3.51 t (4H each, CH_2), 1.11–1.86 m (10H, CH_2, cyclohexyl). Found, %: C 45.16; H 5.21; N 10.15. $C_{16}H_{21}Br_2N_3O$. Calculated, %: C 44.54; H 4.87; N 9.74.

3-Bromo-*N*-isobutyl-5-morpholino-2-nitroso-aniline (VII). 4-(3,5-Dibromo-4-nitrosophenyl)morpholine (**VIa**), 0.35 g (1 mmol), was dissolved in 10 ml of DMF, 0.73 g (10 mmol) of isobutylamine was added to the solution over a period of 5 min, and the mixture was stirred for 3.5 h at 20–25°C. Water, 3 ml, was then added, and the green solid was filtered off, dried, and recrystallized from toluene. Yield 0.29 g (87%), mp 184–185°C. UV spectrum, λ_{max}, nm (logε): 380 (4.38), 670 (1.97). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 12.29 br.s (1H, NH), 2.96 m (2H, CH_2), 1.95 m (1H, CH), 5.59 d and 6.85 d (1H each, H_{arom}, J = 2 Hz), 1.00 d (6H, CH_3, J = 6 Hz), 3.43 t and 3.81 t (4H each, CH_2). Found, %: C 48.85; H 5.83; N 12.17. $C_{14}H_{20}Br_2N_3O_2$. Calculated, %: C 49.12; H 5.84; N 12.28.

1-(3-Bromo-5-morpholino-2-nitrosophenyl)-4-phenylpiperazine (VIII). 4-(3,5-Dibromo-4-nitrosophenyl)morpholine (**VIa**), 0.35 g (1 mmol), was dissolved in 10 ml of DMF, 0.97 g (6 mmol) of *N*-phenylpiperazine was added over a period of 5 min, and the mixture was stirred for 30 min at 20–25°C and diluted with 3 ml of water. The dark green solid was filtered off, dried, and recrystallized from toluene. Yield 0.34 g (81%), mp 153–154°C. UV spectrum, λ_{max}, nm (logε): 385 (4.29), 765 (2.17). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.0–7.30 m (10H, H_{arom}); 6.91 s and 5.93 s (1H each, 4'-H, 6'-H); 3.09 t, 3.45 t, 3.51 t, and 3.83 t (4H each, CH_2). Found, %: C 55.42; H 5.30; N 12.74. $C_{20}H_{23}BrN_4O_2$. Calculated, %: C 55.68; H 5.33; N 12.99.

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