2-Nitroso-*N*-arylanilines: Products of Acid-Promoted Transformation of σ^H Adducts of Arylamines and Nitroarenes

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Abstract: Anions generated from arylamines react with substituted nitrobenzenes to form σ^H adducts, which, under protonation with acetic acid, undergo transformation to 2-nitroso-*N*-arylamines, susceptible to reduction, condensation and cyclization reactions.

Key words: nucleophilic, additions, arenes, amines, nitroso group

The most general reaction of nucleophilic reagents with nitroaromatics is their addition to the electron-deficient positions *ortho* or *para* in the nitroarene with formation of so-called σ adducts.[1] When a good leaving group is located at such position it is often replaced by the nucleophile in the well-known S_NAr substitution process. Unsubstituted positions *ortho* or *para* in the nitroarene are more reactive, but the corresponding σ^H adducts are not prone to simple elimination of hydride anion in the S_NAr process. Nucleophilic substitution of hydrogen requires auxiliary leaving groups located at the nucleophile [vicarious nucleophilic substitution (VNS)][2] or at a side chain of the nitroarene (*cine* and *tele* substitutions),[1a,3] or presence of external oxidants (oxidative nucleophilic substitution of hydrogen) which causes that elimination of a proton instead of a hydride ion takes place.[1,4]

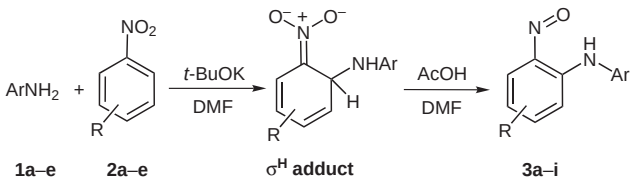
In our studies on the synthesis of polycyclic nitrogen heterocycles, we investigated the reactions of carbanions and other nucleophiles with nitroaromatic compounds, promoted by the Lewis acids, leading to substituted quinoline,[5,6] 1-hydroxyindole[6] or 2,1-benzisoxazole[7] and also more complex polycyclic heterocyclic structures.[8] The common intermediates in these one-pot reactions seem to be the σ^H adducts of the nucleophiles to the nitroarenes, which supposedly undergo transformation to the corresponding nitrosoarenes as a result of base-induced elimination of water, which can be assisted by a proton or a Lewis acid. The whole process can be also considered as a special case of the oxidative nucleophilic substitution of hydrogen (ONSH), in which the intramolecular redox process proceeds with reduction of the nitro group.

The similar Wohl–Aue reaction of an anilide anion with nitroarenes, leading to phenazine derivatives, is also believed to proceed via cyclization of intermediate nitroso compounds, although 2-nitrosodiarylamines have not been detected.[9] On the other hand, when σ^H adducts are formed in the position *para* to the nitro group, the corresponding 4-nitrosodiarylamines can be obtained.[9b,10]

It should be mentioned here, that σ^H adducts of some *tert*-alkylamines to nitrosoarenes undergo intermolecular oxidation with the substrate, or with the external oxidant, producing *ortho* and *para* *N*-(*tert*-alkyl)nitrosoanilines.[11]

In order to acquire more information about the mechanism of the complex reactions of nitroarenes with nucleophiles leading to nitrogen heterocycles, we began to examine it step by step, with special attention paid to the formation of σ^H adducts and their interactions with proton or Lewis acids. From several results of VNS and ONSH reactions published by Mąkosza and co-workers it is known, that under appropriate conditions, σ^H adducts of nucleophiles to mononitroarenes can be formed in considerable concentration, and sometimes even almost quantitatively.[4,12] The *cine* substitution of the nitro group by elimination of HNO_2 from the σ^H adducts of some carbanions and nitrobenzene derivatives, also requires their efficient formation as relatively stable intermediates.[13] The elimination proceeds upon acidification of σ^H adducts with strong aqueous acids. On the other hand, definitely stable σ^H adducts were generated from nitroarenes and alkylmagnesium halides, which, when treated with hydrochloric acid, underwent transformation to alkylated nitrosoarenes.[14]

In this communication we would like to present the results which show that anions of arylamines react with substituted nitrobenzenes to form σ^H adducts and the latter, when protonated with acetic acid, undergo transformation to nitroso compounds, isolated in reasonable yields (Scheme 1).[15]



Scheme 1 Formation of nitrosoanilines **3a**–**i**

The starting anilide anions were generated from aniline derivatives **1a**–**e** in the presence of an excess of *t*-BuOK in DMF at –60 °C, and were subjected to the reaction with substituted nitrobenzenes **2a**–**e**. Then the σ^H adducts were acidified with acetic acid. Usual workup and column chromatography furnished pure products **3a**–**i** (Table 1).

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Table 1 Formation of Nitrosoanilines **3** from Nitroarenes and Substituted Anilines

Entry	Arylamine	Ar	Nitroarene	R	2-Nitroso-*N*-arylaniline	Yield (%)[a]
1	**1a**	4-ClC_6H_4	**2a**	4-Cl	**3a**	64
2	**1b**	4-$EtOC_6H_4$	**2a**	4-Cl	**3b**	66
3	**1c**	3,4-diClC_6H_3	**2a**	4-Cl	**3c**	55
4	**1d**	4-MeC_6H_4	**2a**	4-Cl	**3d**	56
5	**1a**	4-ClC_6H_4	**2b**	2,4-diCl	**3e**	55[b]
6	**1d**	4-MeC_6H_4	**2c**	4-OMe	**3f**	72[c]
7	**1a**	4-ClC_6H_4	**2d**	2-Cl-4-CF_3	**3g**	30
8	**1b**	4-$EtOC_6H_4$	**2e**	2-Cl-4-OMe	**3h**	60
9	**1e**	4-BrC_6H_4	**2c**	4-OMe	**3i**	33

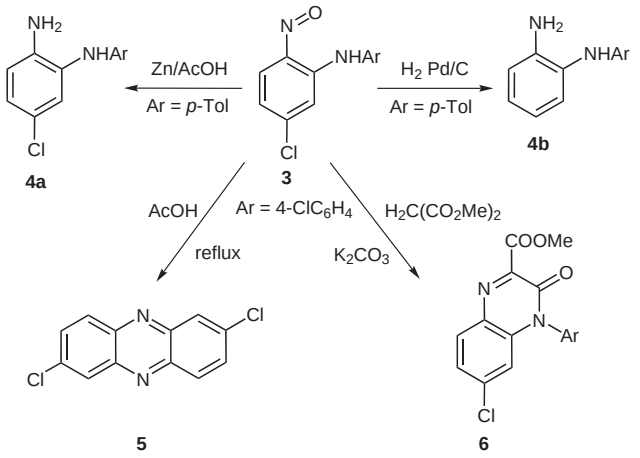
[a] Isolated yield.
[b] *Ortho* chlorine substitution product (19%) was isolated.
[c] The starting nitroarene (12%) was recovered.

The *para* positions in all nitroarenes under investigations were, intentionally, occupied by substituents, thus there was no orientation issue in the formation of σ^H adducts and consequently, only one regioisomer of each nitrosoamine **3** was formed.

Preliminary identification of products **3** was based on their high resolution mass spectra, which revealed the correct elemental composition for molecular ions. ^1H and ^{13}C NMR spectra of the *ortho*-substituted products (**3e**, **3g**, **3h**) are well recognized and are in accordance with the assumed structures. On the other hand, almost all compounds with unsubstituted position *ortho* to the nitroso group (**3a**–**d** and **3i**) show exceptionally broad or even undetectable signals for both *ortho* carbon atoms and also very broad signals for the aromatic *ortho* protons. A question that therefore arose was whether there was a possibility of nitroso/amine–oxime/imine tautomerism. For *ortho* nitrosoanilines reported in the literature, the structure is accepted as correct, although extensive examinations have not been done.[16] Much more inclusive spectral analysis was completed for heterocyclic system of 4-nitroso-5-aminopyrazole[17] and 6-amino-4-methylamino-5-nitrosopyrimidine[18] leading to the similar conclusion. On this basis, one can assume that the observed ^1H and ^{13}C NMR spectra of **3** could be explained considering the dynamic equilibrium between ArNO rotamers[19] of the *ortho*-aminonitrosoarenes. To support this hypothesis, for one of the products (**3f**) both ^1H and ^{15}N GHMBC experiments were performed at lower temperature (–15 °C). They revealed the chemical shift values for ^{15}N to be –268.5 ppm and 334.0 ppm (relative to $MeNO_2$). The former is situated in the nitroso group range, and the latter, showing one-bond N–H coupling (J = 91.9 Hz), proves the presence of the amino group, hence both are in accord with the assumed *ortho*-nitrosoaniline structure and are parallel to those described for *N*-(*tert*-butyl)-2-nitrosoanilines.[11] While we believe that this is also valid for all products **3**, additional spectral studies on their structure and possible tautomerism are considered necessary.

Up to date, 2-nitroso-*N*-arylanilines were reported in the literature only as by-products in the photochemical cyclization of *N*-acyl-2-nitroarylanilines,[16a,b] in the Fisher–Hepp rearrangement[16c] and in a complex mixture of products of the reaction of aryliminodimagnesium reagents with nitroarenes.[16d] The convenient method of their synthesis, presented in this communication, allows to consider them as useful intermediates in organic synthesis, which can be demonstrated by a few representative transformations (Scheme 2). For example, reduction of **3d** was performed, depending on the applied conditions, with preservation (Zn/AcOH) or removal of the halogen atom (H_2, Pd/C) from the aryl ring, which led to *N*-(2-aminoaryl)-*N*-arylamines **4a** (yield 84%) and **4b** (yield 75%), respectively.[15] Acid-catalyzed cyclization of **3a** resulted in the formation of the expected 2,7-dichlorophenazine **5**.[15] Characteristic reactivity of the nitroso group was revealed in the reaction of **3a** with dimethyl malonate in the presence of K_2CO_3, which led to 1-(4-chlorophenyl)-7-chloroquinoxalin-2(1*H*)-one (**6**) via the Ehrlich–Sachs condensation followed by intramolecular acylation of the amine with the ester function.[15]

The title nitrosoanilines can be of interest both for the synthesis of nitrogen-substituted arenes and nitrogen heterocycles, and for the mechanistic elucidation of reactions of nitroarenes with anilides, if they are anticipated as intermediates. Our investigations in both these fields are now in progress.



Scheme 2 Reactions of 2-nitroso-*N*-arylanilines **3**

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(15) Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 instrument (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR spectra) in $CDCl_3$. Chemical shifts (δ) are expressed in ppm referred to TMS, and coupling constants are given in Hz. ^{15}N GHMBC experiment was performed on a Bruker 500 instrument in $CDCl_3$ at 273 K. Mass spectra (EI, 70 eV) were obtained on an AMD-604 spectrometer. Silica gel Merck 60 (230–400 mesh) was used for column chromatography. 2-Chloro-4-trifluoromethylonitrobenzene[20] (**2d**) and 4-chloro-2-methoxynitrobenzene[21] (**2e**) were obtained according to the literature. All other reagents are commercially available.

Preparation of 2-Nitroso-*N*-arylanilines 3a–i; General Procedure

To a cooled solution of *t*-BuOK (6 mmol, 672 mg) in DMF (2 mL) was added dropwise at –60 °C a solution of aniline **1** (2 mmol) in DMF (1 mL) and nitroarene **2** (2 mmol) in DMF (1 mL). The mixture was stirred at this temperature for 2–5 min, and then a cooled mixture of AcOH (1.5 mL) and DMF (1.5 mL) was added in one portion. The cooling bath was removed and the mixture was allowed to reach the ambient temperature, then it was poured into H_2O (ca. 50 mL) and extracted with EtOAc. The extract was washed with H_2O and brine, and dried with Na_2SO_4. After evaporation, the crude product mixture was subjected to column chromatography (SiO_2, hexane–benzene) to obtain products **3a–i**. The representative examples of **3** are described below.

3a: Brown solid; mp 124–125 °C. ^{1}H NMR: δ = 7.09 (dd, *J* = 1.4, 10.2 Hz, 1 H), 7.05 (d, *J* = 1.7, 8.8 Hz, 1 H), 7.17–7.24 (m, 2 H), 7.39–7.45 (m, 2 H), 8.68 (br s, 1 H), 11.82 (br s, 1 H). ^{13}C NMR: δ = 114.0, 119.1, 126.1, 130.0, 132.2, 135.0, 140.4 (br), 144.8, 154.9, one signal not observed. MS (EI): *m*/*z* (%) = 268 (7), 266 (11), 251 (66), 249 (100), 237 (18), 235 (26), 201 (22). HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{12}H_8ON_2{}^{35}Cl_2$: 266.0014; found: 266.0024.

3d: Brown solid; mp 96–97 °C (hexane–benzene). ^{1}H NMR: δ = 2.38 (s, 3 H), 6.93 (d, *J* = 8.6 Hz, 1 H), 7.05 (d, *J* = 2.0 Hz, 1 H), 7.13 (br d, *J* = 8.2 Hz, 2 H), 7.23 (br d, *J* = 8.2 Hz, 2 H), 8.67 (br s, 1 H), 12.08 (br s, 1 H). ^{13}C NMR: δ = 114.4, 118.5, 120.2, 124.9, 130.4, 133.4, 136.9, 141.8 (very br), 144.6, 154.9, one signal not observed. MS (EI): *m*/*z* (%) = 245 (6), 231 (42), 229 (100), 214 (22), 180 (25). HRMS (LSI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{12}ON_2{}^{35}Cl$: 247.0632; found: 247.0621.

3f: Brown solid; mp 106–107 °C. ^{1}H NMR (500 MHz, $CDCl_3$, –15 °C): δ = 2.37 (s, 3 H), 3.76 (s, 3 H), 6.35 (d, *J* = 2.1 Hz, 1 H), 6.57 (dd, *J* = 2.1, 9.2 Hz, 1 H), 7.17–7.25 (m, 4 H), 8.48 (d, *J* = 9.2 Hz, 1 H), 12.97 (br s, 1 H). ^{13}C NMR: δ = 20.9, 55.7, 93.5, 109.3, 124.7, 130.2, 133.9, 136.4, 137.7, 142.4, 153.6, 167.0. ^{15}N NMR (GHMBC, $CDCl_3$, δ relative to $MeNO_2$, 273 K): δ = –286.5 (N=O), 334 (J_{NH} = 91.9 Hz, NH). MS (EI): *m*/*z* (%) = 242 (16), 241 (15), 225 (100), 210 (15), 196 (15), 182 (21). HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{14}O_2N_2$: 242.1055; found: 242.1051.

Reduction of 3d with Zn/AcOH: To a solution of 2-nitroso-*N*-(4-tolyl)aniline **3d** (0.15 mmol, 37.2 mg) in AcOH (1 mL), powdered Zn (150 mg) was added and the mixture was stirred at ambient temperature, while monitored by TLC. After the substrate had disappeared (ca. 1.5 h), the mixture was diluted with EtOAc (10 mL), filtered, washed with H_2O, sat. $NaHCO_3$ and H_2O, and then dried with Na_2SO_4. The solvent was evaporated and the crude product was purified by column chromatography (SiO_2, hexane–EtOAc, 5:1) to give **4a** (26.2 mg, 75%).

4a: Brown solid; mp 65–66 °C(hexane) [Lit.[22] 66.5–67.5 °C (PE)]. ^{1}H NMR: δ = 2.68 (s, 3 H), 3.64 (br s, 2 H), 5.10 (br s, 1 H), 6.69 (d, *J* = 8.4 Hz, 1 H), 6.72–6.76 (m, 2 H), 6.89 (dd, *J* = 2.3, 8.4 Hz, 1 H), 7.04–7.08 (m, 3 H). ^{13}C NMR: δ = 20.6, 116.9, 117.0, 121.7, 123.7, 123.8, 129.9, 130.0, 131.5, 138.6, 141.3. MS (EI): *m*/*z* (%) = 232 (100), 217 (59). HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{13}N_2{}^{35}Cl$: 232.0767; found: 232.0772.

Catalytic Hydrogenation of 3d: 2-Nitroso-*N*-(4-tolyl)aniline **3d** (0.22 mmol, 55 mg), suspended (partially soluble) in MeOH (1 mL), Et_3N (0.44 mmol, 44 mg) and Pd/C (10%, 25 mg) were stirred under H_2 at r.t. for 30 min. The catalyst was filtered off and the solution was evaporated to dryness. The residue was diluted with EtOAc (10 mL) and H_2O (5 mL), and the organic layer was separated, washed with H_2O and dried with Na_2SO_4. After evaporation of the solvents, the crude product was purified by column chromatography (SiO_2, hexane–EtOAc, 4:1) to deliver **4b** (37 mg, 84%).

4b: Brown solid; mp 77 °C(hexane). ^{1}H NMR: δ = 2.26 (s, 3 H), 3.67 (br s, 2 H), 5.26 (br s, 1 H), 6.65 (m, 2 H), 6.71–6.76 (m, 1 H), 6.78 (dd, *J* = 1.2, 7.8 Hz, 1 H), 6.95–7.00 (m, 1 H), 7.00–7.05 (m, 2 H), 7.08 (dd, *J* = 1.4, 7.8 Hz, 1 H). ^{13}C NMR: δ = 20.4, 115.8, 116.1, 119.1, 123.8, 125.0, 128.8, 129.4, 129.8, 141.3, 142.62. MS (EI): *m*/*z* (%) = 198 (100), 183 (64), 91 (18). HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{14}N_2$: 198.1157; found: 198.1147.

Cyclization of 3a to 2,7-Dichlorophenazine (5): 2-Nitroso-*N*-(4-chlorophenyl)aniline **3a** (0.1 mmol, 25 mg) in AcOH (3 mL) was refluxed for 1.5 h. After cooling down, the mixture was diluted with H_2O and the precipitated crude product was filtered off. Recrystallization from EtOH gave pure **5** (20 mg (80%).

5: Pale yellow solid; mp 265–266 °C (Lit.[23] 266–268 °C). MS (EI): *m*/*z* (%) = 250 (64), 248 (100), 213 (33).

Condensation of 3a with Methyl Malonate: 2-Nitroso-*N*-(4-chlorophenyl)aniline **3a** (0.067 mmol, 18 mg), methyl malonate (0.14 mmol, 18 mg) and K_2CO_3 (75 mg) were stirred in MeCN (1 mL) at r.t. for 30 min. The mixture was diluted with MeCN, filtered and evaporated. The crude product was purified by column chromatography (SiO_2, hexane–EtOAc, 5:1) to obtain pure **6** (20 mg, 85%).

6: Yellowish crystals; mp 160–161 °C. ^{1}H NMR: δ = 4.03 (s, 3 H), 6.71 (d, *J* = 2.2 Hz, 1 H), 7.23–7.27 (m, 2 H), 7.35 (dd, *J* = 2.2, 8.6 Hz, 1 H), 7.60–7.65 (m, 2 H), 7.92 (d, *J* = 8.6 Hz, 1 H). ^{13}C NMR: δ = 55.3, 115.2, 125.2, 129.5, 130.2, 130.9, 132.1, 132.8, 135.5, 136.3, 138.9, 148.8, 151.8, 163.4. MS (EI): *m*/*z* (%) = 350 (31), 348 (48), 263 (67), 261 (100), 226 (24), 191 (21). HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{16}H_{10}N_2O_3{}^{35}Cl_2$: 348.0068; found: 348.0076.

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