

Regioselective Aromatic Nucleophilic Substitution in *N*-Aryl-2-nitrosoanilines with Oxygen and Nitrogen Nucleophiles

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Abstract: Aromatic nucleophilic substitution of halogens in *N*-aryl-2-nitrosoanilines with ammonia, alkylamines and alkoxide ions proceeds efficiently and highly regioselectively in the position *para* to the nitroso group. When two halogen atoms *ortho* and *para* are present, the latter is substituted exclusively. Oxidative substitution of hydrogen at the unsubstituted *ortho* position of the nitrosoaniline ring does not compete with substitution of *para* halogen atoms. The reaction allows the synthesis of *N*-aryl-2-nitrosoanilines which cannot be obtained according to known methods.

Key words: arenes, amines, nucleophilic aromatic substitution, regioselectivity, nitroso group

The main reaction pathway between nucleophilic agents and electron-deficient arenes is addition to the ring in activated positions. If there is a nucleofugal group X (Cl, OMe, etc.) in one of such positions, the addition can result in the formation of σ^{H} - and σ^{X} -adducts. It has been unambiguously shown that the rate of the former process is faster than formation of σ^{X} -adducts. Since the addition is associated with dearomatization of the ring, the σ -adducts tend to restore aromaticity. Fast departure of X⁻ from σ^{X} -adducts results in nucleophilic aromatic substitution (S_NAr).^{1,2} Spontaneous departure of H⁻ from σ^{H} -adducts does not occur but these adducts can be transformed into products of nucleophilic substitution of hydrogen (S_N^HAr) in several ways,^{1c,3,4} and under suitable circumstances this process dominates over the conventional S_NAr reaction.⁴

A few years ago we described nucleophilic substitution of hydrogen in the reaction of nitroarenes with anilines in the presence of a strong base. The reaction, in which σ^{H} -adducts are converted into substituted nitrosoarenes according to an intramolecular redox stoichiometry, allowed for the synthesis of a wide range of *N*-aryl-2-nitrosoanilines.⁵ The reaction is a general and practical method for the preparation of these compounds⁵⁻⁹ which are otherwise difficult to obtain. This simple and one-step synthesis of *N*-aryl-2-nitrosoanilines is of great value because such compounds are versatile starting materials for the synthesis of a plethora of heterocyclic systems, for example, phenazines,⁶ benzimidazoles⁷ and quinoxalinones.⁸

Although the scope of the nucleophilic substitution of hydrogen in nitroarenes with anilines to form *N*-aryl-2-nitrosoanilines is rather wide, there are some limitations. The

reaction proceeds efficiently with nitroarenes of sufficient electrophilic activity, however, it does not proceed if the nitroarenes contain electron-donating substituents, such as NR₂, OR and particularly NHR or OH, that form anions under the reaction conditions. Since *N*-aryl-2-nitrosoanilines with such electron-donating substituents can be starting materials in the synthesis of valuable heterocycles, it was of interest to expand our methods to these nitrosoanilines. It is well known that the nitroso group is a strong electron-withdrawing substituent, even stronger than the nitro group. Thus, we expected that it would be possible to introduce alkylamino, alkoxy and similar substituents into *N*-aryl-2-nitrosoanilines, obtained from electron-deficient nitroarenes, via nucleophilic substitution of hydrogen or halogen atoms.

Despite the strong electron-withdrawing effect of the nitroso group, nucleophilic substitution of halogen (S_NAr reaction) or hydrogen (S_N^HAr) in nitrosoarenes has only been sporadically reported.¹⁰⁻¹² Indeed, nitrosoarenes are rather unstable, due to their facile dimerization and redox processes, they are not readily available and nucleophiles tend to add to the nitrogen of the nitroso group.¹³

Since *N*-aryl-2-nitrosoanilines have two activated positions, the 3- and 5-positions (*ortho* and *para* to the nitroso group, respectively), nucleophilic agents can add to the ring at both of them, regardless what substituents are present at these positions. Addition at the position bearing any leaving group would result in replacement of this group with the nucleophile (S_NAr reaction), while addition to the unsubstituted ring position, which seems to be faster than to any substituted position, may result in oxidative substitution of hydrogen. All these reaction pathways, reported for halonitrosoarenes,¹⁰⁻¹³ are also likely in the case of *N*-aryl-2-nitrosoanilines (Scheme 1).

Preliminarily studied reactions of three differently substituted *N*-aryl-2-nitrosoanilines **1** that contain chlorine in one or both activated positions with nucleophiles, such as methoxide ion and alkylamines, revealed a striking difference in reactivity of the 3- and 5-positions in the substitution of halogen, and a low tendency to substitute hydrogen. In the reaction of **1a** (X = Cl, Y = H, Ar = 4-ClC₆H₄), only substitution of the 5-chlorine was observed. Substitution of the 3-chlorine in **1b** (X = H, Y = Cl, Ar = 2,6-Me₂C₆H₃) occurred with methoxide ion to give *N*-(2,6-dimethylphenyl)-3-methoxy-2-nitrosoaniline, whereas the reactions with amines gave mixtures of unidentified products. The reactions of dichloro compound

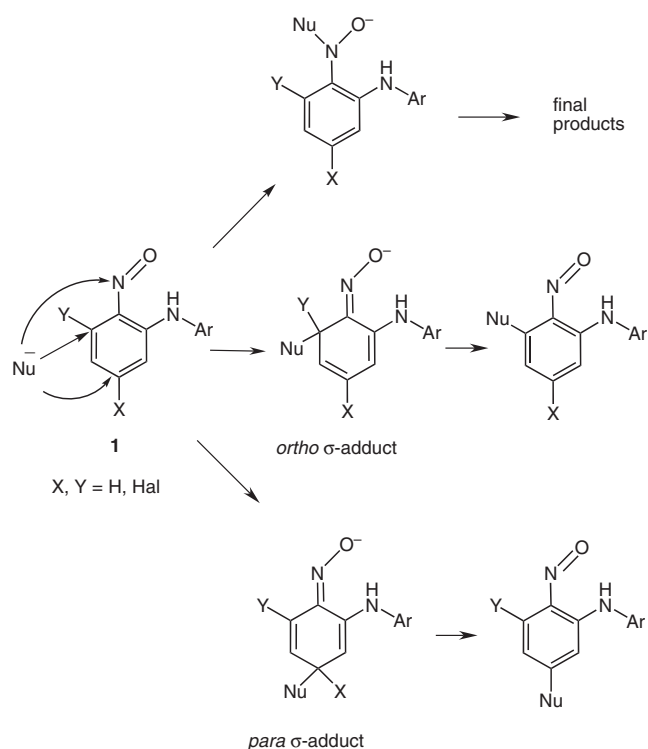
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1c (X = Y = Cl, Ar = 4-EtOC₆H₄) with all examined nucleophiles proceeded selectively with substitution of the 5-chlorine, and no reaction at the nitroso group was observed.



Scheme 1 Possible ways of nucleophilic addition to *N*-aryl-2-nitrosoanilines

The high regioselectivity in the nucleophilic substitution of **1** may be advantageous for the synthesis of a variety of substituted 2-nitrosoanilines. In order to examine the potential value of the method, several *N*-aryl-2-nitrosoanilines **1a–j**, possessing one or two halogen atoms in the 3- and/or 5-position activated by the nitroso group, were subjected to the reaction with ammonia, and primary and secondary amines, as well as alcohols (Table 1). The reactions with alcohols, used also as the solvent, were promoted by potassium carbonate. Amines were used in a fivefold excess and the reactions were carried out in acetonitrile. For introduction of the unsubstituted amino group, a 4 M ethanolic solution of ammonia was used. All the reactions proceeded at ambient temperature, for the time specified in Table 1.

Substitution of 5-fluoro and 5-chloro derivatives with alkoxides and secondary amines gave products **2** in high yields. Relatively less nucleophilic primary alkylamines reacted slower, much more efficiently with 5-fluoro- than with 5-chloro-*N*-aryl-2-nitrosoanilines. On the other hand, more reactive morpholine was able to substitute the 5-methoxy group in **1e**, although after long reaction time. Noteworthy, condensation of primary amines with the nitroso group was never observed.

The only serious side process observed was cyclization of **1a** and **1g** with formation of phenazine derivatives in the

reactions carried out in the potassium carbonate/methanol system (Table 1, entries 1 and 16). In a few other reactions of **1** carried out under such conditions, this cyclization was also observed, but amounts of the resultant phenazines were rather insignificant.

The cyclization of *N*-aryl-2-nitrosoanilines in the presence of potassium carbonate in methanol has been described previously, and is an efficient method for the synthesis of certain phenazine derivatives.⁶ Interestingly, if 2-nitrosoaniline is *N*-substituted with a condensed, bicyclic aromatic system (1-naphthalene or 8-quinoline) the cyclization is so fast that possible substitution of 4-chlorine was not observed.⁶ Detailed studies on the reactivity and selectivity of the cyclization under various conditions are currently in progress.

The results given in Table 1 confirmed the main feature of the reaction which was revealed in the introductory examination, i.e. the high preference for the substitution of the halogen located *para* to the nitroso group, over that located *ortho*. When both the 3- and 5-positions were occupied by chlorine atoms, only the latter was replaced (Table 1, entries 4–6, and 14 and 15). This regioselectivity of the substitution in **1** is consistent and was observed for all nucleophiles studied (neutral alkylamines and alkoxide ions), hence it is apparently an inherent feature of the *ortho*-aminonitrosobenzene system. It seems to be caused by efficient conjugation of the lone electron pair of the *ortho*-amine nitrogen of the *N*-aryl-2-nitrosoanilines with the strong electron-withdrawing nitroso group (Figure 1). In the favored quinoid structure, the 3- and 5-positions are markedly differentiated regarding their electrophilic activity, and addition of a nucleophile occurs preferentially to the 5-position.

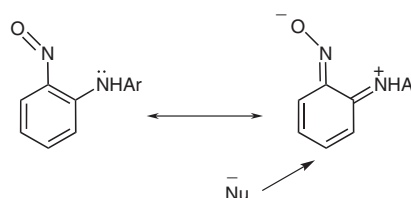
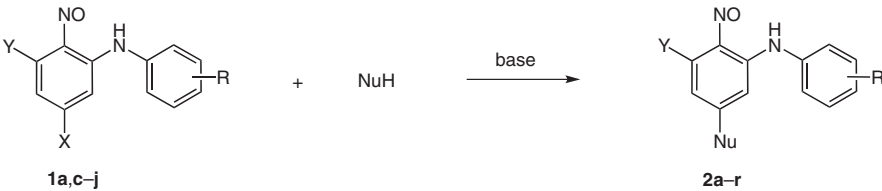


Figure 1

Similar directing effects caused by the conjugation of electron pairs of heteroatoms with a nitro group in nitroarenes have been observed previously in reactions of carbanions with 2,4-dinitrophenolates,¹⁴ 2,4-dinitroaniline derivatives¹⁵ and *N*-substituted 2-nitropyrroles¹⁶ (Figure 2). In all these cases, reorganization of the electronic structure of the substrate, caused by conjugation, led to selective or preferential addition of carbanions of aryl chloromethyl sulfones to the most electrophilic position of the ring.

The known literature data dealing with nucleophilic substitution in nitrosoarenes give rather limited information on the regioselectivity of the reaction. In polyhalogenated

Table 1 Reaction of *N*-Aryl-2-nitrosoanilines **1** with Nucleophiles


Entry	X	Y	R	1	NuH	Conditions	Time ^a (h)	2	Yield ^b (%)
1	Cl	H	4-Cl	a	MeOH	K ₂ CO ₃ , MeOH, r.t.	2	a	27 ^c
2	Cl	H	4-Cl	a	pyrrolidine	MeCN, r.t.	2	b	85
3	Cl	H	4-Cl	a	<i>n</i> -BuNH ₂	MeCN, r.t.	7 d	c	86
4	Cl	Cl	4-OEt	c	MeOH	K ₂ CO ₃ , MeOH, r.t.	2	d	81
5	Cl	Cl	4-OEt	c	pyrrolidine	MeCN, r.t.	1	e	85
6	Cl	Cl	4-OEt	c	<i>n</i> -BuNH ₂	MeCN, r.t.	44	f	74
7	F	H	4-Cl	d	<i>n</i> -BuNH ₂	MeCN, r.t.	2	c	84
8	F	H	4-Cl	d	morpholine	MeCN, r.t.	1	g	95
9	F	H	4-Cl	d	BnNH ₂	Et ₃ N, MeCN, r.t.	7	h	87
10	F	H	4-Cl	d	HO(CH ₂) ₂ NH ₂	MeCN, r.t.	2	i	85
11	F	H	4-Cl	d	NH ₃	EtOH, r.t.	24	j	90
12	Cl	H	4-Cl	a	morpholine	MeCN, r.t.	2	g	81
13	OMe	H	4-Cl	e	morpholine	MeCN, r.t.	22 d	g	74
14	Cl	Cl	4-Cl	f	morpholine	MeCN, r.t.	24	k	88
15	Cl	Cl	4-Cl	f	MeOH	K ₂ CO ₃ , MeOH, r.t.	4	l	78
16	Cl	H	H	g	MeOH	K ₂ CO ₃ , MeOH, r.t.	3	m	53 ^d
17	Cl	OMe	H	h	MeOH	K ₂ CO ₃ , MeOH, r.t.	2	n	96
18	F	H	4-F	i	HO(CH ₂) ₂ OH	K ₂ CO ₃ , glycol, r.t.	2	o	86
19	F	H	4-F	i	CH ₂ =CHCH ₂ NH ₂	MeCN, r.t.	2	p	76
20	Cl	OMe	4-OEt	j	pyrrolidine	MeCN, r.t.	3	q	90
21	Cl	OMe	4-OEt	j	MeOH	K ₂ CO ₃ , MeOH, r.t.	7	r	81

^a Not optimized; d = days.^b Yield of isolated products.^c Additionally, 2,6-dichlorophenazine (28%) was formed.^d Additionally, 2-chlorophenazine (22%) was formed.

nitrosobenzenes, substitution of both *ortho*¹⁰ and *para*¹¹ halogens with nucleophiles was observed. Noteworthy, when the halonitrosoarene possesses an activated unsubstituted position, spontaneous oxidative substitution of hydrogen was much faster than the S_NAr reaction of halogens.^{10,12}

As indicated by the results in Table 1, substitution of hydrogen at the unoccupied 3-position in **1** was not observed, even when an inactive nucleofugal group such as methoxy was present at the 5-position (Table 1, entry 13).

In conclusion, the presented method allows the synthesis of *N*-aryl-2-nitrosoanilines which are difficult or impossible to obtain directly by nucleophilic substitution of hydrogen in nitroarenes with anions of anilines.⁵ It extends the scope of available compounds potentially useful in the synthesis of many important heterocyclic systems. Aromatic nucleophilic substitution of halogens in activated positions of *N*-aryl-2-nitrosoanilines proceeds efficiently with various neutral and anionic nucleophiles under very mild conditions; moreover, it is highly regioselective. When two halogens *ortho* and *para* to the nitroso group

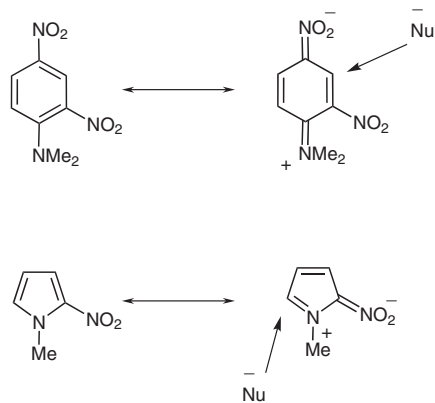


Figure 2

are present, the *para* halogen is substituted exclusively. Oxidative substitution of hydrogen at activated, but unsubstituted, positions of the nitrosoarene ring, common in reactions of polyhalonitrosoarenes, does not compete with substitution of *para* halogens. As a consequence, the reaction is clean and high-yielding.

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian VNMRs 500 instrument (500 MHz for ^1H and 125 MHz for ^{13}C spectra) at 298 K (except for **2i**, which were obtained at 353 K). Chemical shifts (δ) are expressed in ppm referred to TMS; coupling constants are in hertz. Mass spectra (EI, 70 eV) were obtained on an AMD-604 spectrometer. Silica gel 60 (Merck, 230–400 mesh) was used for column chromatography. MeCN was dried over CaH_2 , distilled and stored over molecular sieves. THF was distilled from a sodium benzophenone ketyl solution. Known *N*-aryl-2-nitrosoanilines **1** were obtained following procedures published previously.⁵

N-Aryl-2-nitrosoanilines **1b** and **1i**; General Procedure

To a cooled soln of *t*-BuOK (695 mg, 6.2 mmol) in anhyd THF (10 mL) was added dropwise at -70 to -78 °C a soln of the aniline (1.77 mmol) in THF (2 mL), then the nitroarene (1.77 mmol) in THF (2 mL). The mixture was stirred at that temperature for 30 min, then poured into sat. aq NH_4Cl (100 mL) and extracted with EtOAc (3×50 mL). The combined extracts were washed with H_2O (100 mL) and brine (80 mL), then dried with Na_2SO_4 , and the solvent was evaporated. The product was isolated by column chromatography.

3-Chloro-*N*-(2,6-dimethylphenyl)-2-nitrosoaniline (**1b**)

Chromatography eluent: CH_2Cl_2 –hexane, 1:10 \rightarrow 2:1.

Dark green solid; yield: 194 mg (42%); mp 110–111 °C.

^1H NMR (500 MHz, CDCl_3): δ = 2.07 (s, 6 H), 6.27 (dd, J = 8.9, 1.0 Hz, 1 H), 7.01 (dd, J = 7.4, 1.0 Hz, 1 H), 7.12–7.15 (m, 2 H), 7.17–7.22 (m, 2 H), 12.58 (s, 1 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 18.0, 115.0, 118.0, 128.1, 128.7, 133.2, 135.3, 135.7, 138.6, 144.7, 152.5.

MS (EI, 70 eV): m/z (%) = 260 (49), 245 (100), 228 (73), 194 (67).

HRMS (EI): m/z calcd for $\text{C}_{14}\text{H}_{13}\text{N}_2\text{O}^{35}\text{Cl}$: 260.0716; found: 260.0730.

5-Fluoro-*N*-(4-fluorophenyl)-2-nitrosoaniline (**1i**)

Chromatography eluent: hexane–EtOAc, 4:1.

Green solid; yield: 246 mg (59%); mp 100–101 °C.

^1H NMR (500 MHz, CDCl_3): δ = 6.55–6.60 (m, 1 H), 6.68–6.78 (m, 1 H), 7.11–7.17 (m, 2 H), 7.20–7.24 (m, 2 H), 8.83 (br s, 1 H), 12.11 (br s, 1 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 99.5 (d, $J_{\text{C-F}}$ = 27 Hz), 107.5 (d, $J_{\text{C-F}}$ = 25 Hz), 116.8 (d, $J_{\text{C-F}}$ = 24 Hz), 127.1 (d, $J_{\text{C-F}}$ = 7 Hz), 132.3, 135.9, 145.0, 154.8, 161.2 (d, $J_{\text{C-F}}$ = 246 Hz), 168.1 (d, $J_{\text{C-F}}$ = 260 Hz).

MS (EI, 70 eV): m/z (%) = 234 (19), 220 (30), 217 (100), 203 (97).

HRMS (EI): m/z calcd for $\text{C}_{12}\text{H}_8\text{N}_2\text{O}_2\text{F}_2$: 234.0605; found: 234.0601.

Reaction of *N*-Aryl-2-nitrosoanilines **1** with Alcohols; General Procedure

A *N*-aryl-2-nitrosoaniline **1** (0.5 mmol) was dissolved in the appropriate alcohol (5 mL), anhyd K_2CO_3 (953 mg, 6.8 mmol) was added and the mixture was stirred magnetically at r.t. for the time specified in Table 1. The mixture was then poured into H_2O (50 mL) and extracted with EtOAc (3×50 mL). The combined extracts were washed with H_2O (100 mL) and brine (70 mL), then dried with Na_2SO_4 , and the solvent was evaporated. The crude product was purified by silica gel column chromatography (hexane–EtOAc, 4:1 to 1:1, unless otherwise specified) to obtain pure **2**.

Reaction of *N*-Aryl-2-nitrosoanilines **1** with Amines; General Procedure

A *N*-aryl-2-nitrosoaniline **1** (0.5 mmol) was dissolved in MeCN (10 mL) and the appropriate amine (2.5 mmol) was added, except for benzylamine (64 mg, 0.6 mmol) added along with Et_3N (121 mg, 1.2 mmol). The mixture was stirred at r.t. for the time specified in Table 1. After the reaction was complete, the mixture was poured into H_2O (50 mL) and extracted with EtOAc (3×50 mL). The combined extracts were washed with H_2O (100 mL) and brine (50 mL), then dried with Na_2SO_4 , and the solvent was evaporated. The crude product was purified by silica gel column chromatography (hexane–EtOAc, 4:1 \rightarrow 1:1, unless otherwise specified) to obtain pure **2**.

Reaction of *N*-Aryl-2-nitrosoaniline **1d** with Ammonia

N-(4-Chlorophenyl)-5-fluoro-2-nitrosoaniline (**1d**; 150 mg, 0.6 mmol) was dissolved in 4 M NH_3 in EtOH (7 mL) and the reaction mixture was kept at r.t. for 24 h, then diluted with H_2O (50 mL) and extracted with EtOAc (3×50 mL). The combined extracts were washed with H_2O (100 mL) and brine (80 mL), then dried with Na_2SO_4 , and the solvent was evaporated. The crude product was purified by silica gel column chromatography (hexane–EtOAc, 2:1) to obtain pure **2j**; yield: 133 mg (90%).

N-(4-Chlorophenyl)-5-methoxy-2-nitrosoaniline (**2a**)

Chromatography eluent: CH_2Cl_2 –EtOAc, 4:1.

Dark solid; yield: 35 mg (27%); mp 110–111 °C.

^1H NMR (500 MHz, CDCl_3): δ = 3.81 (s, 3 H), 6.34 (br s, 1 H), 6.59–6.65 (m, 1 H), 7.20–7.24 (m, 2 H), 7.37–7.41 (m, 2 H), 8.56–8.64 (m, 1 H), 12.77 (s, 1 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 55.9, 93.8, 109.3, 126.1, 129.9, 131.8, 135.6, 136.7, 143.1, 153.8, 167.2.

MS (EI, 70 eV): m/z (%) = 262 (30), 245 (100), 216 (16), 202 (13).

HRMS (EI): m/z calcd for $\text{C}_{13}\text{H}_{11}\text{N}_2\text{O}_2^{35}\text{Cl}$: 262.0509; found: 262.0510.

N-(4-Chlorophenyl)-2-nitroso-5-(pyrrolidin-1-yl)aniline (**2b**)

Green solid; yield: 128 mg (85%); mp 200–202 °C.

^1H NMR (500 MHz, CDCl_3): δ = 2.01–2.07 (m, 4 H), 3.2–3.7 (m, 4 H), 5.86 (d, J = 2.2 Hz, 1 H), 6.38 (dd, J = 9.3, 2.2 Hz, 1 H), 7.21–7.25 (m, 2 H), 7.32–7.36 (m, 2 H), 8.15 (d, J = 9.3 Hz, 1 H), 13.12 (s, 1 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 25.2, 48.3, 89.1, 107.7, 125.7, 129.6, 130.6, 136.9, 138.9, 142.1, 151.8, 153.5.

MS (EI, 70 eV): m/z (%) = 301 (81), 287 (100), 285 (21), 270 (39).
HRMS (EI): m/z calcd for $C_{16}H_{16}N_3O^{35}Cl$: 301.0982; found: 301.0985.

***N*¹-Butyl-*N*³-(4-chlorophenyl)-4-nitrosobenzene-1,3-diamine (2c)**

Dark solid; yield: 130 mg (86%); mp 167–168 °C.

¹H NMR (500 MHz, CDCl₃): δ = 0.94 (t, J = 7.7 Hz, 3 H), 1.36–1.44 (m, 2 H), 1.58–1.64 (m, 2 H), 3.12–3.18 (m, 2 H), 5.31 (br s, 1 H), 5.89 (d, J = 2.1 Hz, 1 H), 6.27–6.31 (m, 1 H), 7.19–7.23 (m, 2 H), 7.32–7.36 (m, 2 H), 8.08 (d, J = 9.1 Hz, 1 H), 13.35 (br s, 1 H).

¹³C NMR (125 MHz, CDCl₃): δ = 13.7, 20.0, 31.0, 42.9, 87.7, 109.6, 125.9, 129.6, 130.9, 136.4, 139.9, 141.7, 151.9, 155.7.

MS (EI, 70 eV): m/z (%) = 303 (100), 286 (78), 229 (77), 209 (29).
HRMS (EI): m/z calcd for $C_{16}H_{18}N_3O^{35}Cl$: 303.1138; found: 303.1135.

3-Chloro-*N*-(4-ethoxyphenyl)-5-methoxy-2-nitrosoaniline (2d)^{5b}

Dark solid; yield: 124 mg (81%).

¹H NMR (500 MHz, CDCl₃): δ = 1.44 (t, J = 7.0 Hz, 3 H), 3.74 (s, 3 H), 4.05 (q, J = 7.0 Hz, 2 H), 6.13 (d, J = 2.4 Hz, 1 H), 6.65 (d, J = 2.4 Hz, 1 H), 6.91–6.95 (m, 2 H), 7.12–7.16 (m, 2 H), 13.55 (br s, 1 H).

¹³C NMR (125 MHz, CDCl₃): δ = 14.8, 56.0, 63.8, 92.9, 110.4, 115.5, 126.9, 128.6, 140.0, 146.1, 149.6, 157.9, 166.8.

MS (EI, 70 eV): m/z (%) = 306 (66), 289 (80), 261 (100), 246 (42).
HRMS (EI): m/z calcd for $C_{15}H_{15}N_2O_3^{35}Cl$: 306.0771; found: 306.0762.

3-Chloro-*N*-(4-ethoxyphenyl)-2-nitroso-5-(pyrrolidin-1-yl)aniline (2e)

Dark solid; yield: 147 mg (85%); mp 170–172 °C.

¹H NMR (500 MHz, CDCl₃): δ = 1.43 (t, J = 6.8 Hz, 3 H), 1.98–2.06 (m, 4 H), 3.06–3.66 (m, 4 H), 4.04 (q, J = 6.8 Hz, 2 H), 5.61 (d, J = 2.4 Hz, 1 H), 6.50 (d, J = 2.4 Hz, 1 H), 6.87–6.91 (m, 2 H), 7.13–7.17 (m, 2 H), 13.49 (br s, 1 H).

¹³C NMR (125 MHz, CDCl₃): δ = 14.8, 25.1, 48.2, 63.7, 88.1, 108.1, 115.2, 126.6, 130.0, 141.7, 145.7, 147.9, 153.0, 157.1.

MS (EI, 70 eV): m/z (%) = 345 (100), 331 (29), 300 (58), 285 (19).
HRMS (EI): m/z calcd for $C_{18}H_{20}N_3O_2^{35}Cl$: 345.1244; found: 345.1235.

***N*¹-Butyl-5-chloro-*N*³-(4-ethoxyphenyl)-4-nitrosobenzene-1,3-diamine (2f)**

Dark brown solid; yield: 128 mg (74%); mp 172–175 °C.

¹H NMR (500 MHz, CDCl₃): δ = 0.92 (t, J = 7.3 Hz, 3 H), 1.32–1.41 (m, 2 H), 1.43 (t, J = 7.0 Hz, 3 H), 1.53–1.61 (m, 2 H), 3.05–3.12 (m, 2 H), 4.04 (q, J = 7.0 Hz, 2 H), 5.10 (br s, 1 H), 5.67 (d, J = 2.2 Hz, 1 H), 6.39–6.42 (m, 1 H), 6.89–6.93 (m, 2 H), 7.12–7.16 (m, 2 H), 13.72 (s, 1 H).

¹³C NMR (125 MHz, CDCl₃): δ = 13.7, 14.8, 20.0, 30.9, 42.9, 63.7, 87.0, 109.5, 115.3, 126.7, 129.6, 142.6, 145.3, 147.9, 155.0, 157.4.

MS (EI, 70 eV): m/z (%) = 347 (59), 333 (100), 302 (45), 290 (68).
HRMS (EI): m/z calcd for $C_{18}H_{22}N_3O_2^{35}Cl$: 347.1401; found: 347.1403.

***N*-(4-Chlorophenyl)-5-(morpholin-4-yl)-2-nitrosoaniline (2g)**

Dark solid; yield: 151 mg (95%); mp 191–192 °C.

¹H NMR (500 MHz, CDCl₃): δ = 3.39–3.42 (m, 4 H), 3.78–3.82 (m, 4 H), 6.11 (d, J = 2.2 Hz, 1 H), 6.59 (dd, J = 9.4, 2.2 Hz, 1 H), 7.18–7.22 (m, 2 H), 7.34–7.38 (m, 2 H), 8.33 (d, J = 9.4 Hz, 1 H), 12.90 (s, 1 H).

¹³C NMR (125 MHz, CDCl₃): δ = 44.7, 66.2, 90.9, 106.8, 126.0, 129.8, 131.2, 136.2, 137.9, 142.3, 152.3, 156.0.

MS (EI, 70 eV): m/z (%) = 317 (100), 300 (72), 228 (36).

HRMS (EI): m/z calcd for $C_{16}H_{16}N_3O_2^{35}Cl$: 317.0931; found: 317.0926.

***N*¹-Benzyl-*N*³-(4-chlorophenyl)-4-nitrosobenzene-1,3-diamine (2h)**

Dark solid; yield: 147 mg (87%); mp 194–196 °C.

¹H NMR (500 MHz, CDCl₃): δ = 4.36 (d, J = 5.4 Hz, 2 H), 5.30 (br s, 1 H), 5.87 (d, J = 2.2 Hz, 1 H), 6.34 (dd, J = 9.1, 2.2 Hz, 1 H), 6.95–7.01 (m, 2 H), 7.22–7.25 (m, 3 H), 7.32–7.41 (m, 4 H), 8.20 (d, J = 9.1 Hz, 1 H), 13.20 (br s, 1 H).

¹³C NMR (125 MHz, CDCl₃): δ = 47.5, 125.7, 127.2, 128.0, 128.5, 128.8, 129.0, 129.6, 130.9, 136.2, 136.6, 138.8, 142.1, 152.4, 154.8.

MS (EI, 70 eV): m/z (%) = 337 (80), 320 (34), 91 (100).

HRMS (EI): m/z calcd for $C_{19}H_{16}N_3O^{35}Cl$: 337.0982; found: 337.0987.

2-({3-[(4-Chlorophenyl)amino]-4-nitrosophenyl}amino)ethanol (2i)

Dark solid; yield: 124 mg (85%); mp 165–167 °C.

¹H NMR (500 MHz, DMSO-*d*₆, 353 K): δ = 3.22 (t, J = 5.8 Hz, 2 H), 3.57 (t, J = 5.8 Hz, 2 H), 4.57 (br s, 1 H), 6.11 (br s, 1 H), 6.45 (br s, 1 H), 7.32–7.44 (m, 4 H), 7.61 (br s, 1 H), 7.96 (br s, 1 H), 13.06 (br s, 1 H).

¹³C NMR (125 MHz, DMSO-*d*₆, 353 K): δ = 44.9, 59.1, 88.0, 108.2, 124.8, 128.9, 137.1, 140.9, 151.6, 156.5.

MS (EI, 70 eV): m/z (%) = 291 (100), 274 (68), 229 (65).

HRMS (EI): m/z calcd for $C_{14}H_{14}N_3O_2^{35}Cl$: 291.0774; found: 291.0780.

***N*³-(4-Chlorophenyl)-4-nitrosobenzene-1,3-diamine (2j)**

Dark red solid; yield: 133 mg (90%); mp 197 °C.

¹H NMR (500 MHz, DMSO-*d*₆): δ = 4.71 (s, 2 H), 5.99 (d, J = 2.2 Hz, 1 H), 6.32 (dd, J = 9.0, 2.2 Hz, 1 H), 7.17–7.21 (m, 2 H), 7.34–7.38 (m, 2 H), 8.28 (d, J = 9.0 Hz, 1 H), 12.95 (s, 1 H).

¹³C NMR (125 MHz, DMSO-*d*₆): δ = 91.7, 108.9, 126.3, 129.7, 131.4, 136.1, 138.8, 143.3, 152.8, 155.1.

MS (EI, 70 eV): m/z (%) = 247 (56), 230 (100), 216 (54).

HRMS (EI): m/z calcd for $C_{12}H_{10}N_3O^{35}Cl$: 247.0512; found: 247.0506.

3-Chloro-*N*-(4-chlorophenyl)-5-(morpholin-4-yl)-2-nitrosoaniline (2k)

Brown solid; yield: 154 mg (88%); mp 210 °C.

¹H NMR (500 MHz, CDCl₃): δ = 3.37–3.40 (m, 4 H), 3.77–3.81 (m, 4 H), 5.96 (d, J = 2.5 Hz, 1 H), 6.71 (d, J = 2.5 Hz, 1 H), 7.16–7.20 (m, 2 H), 7.34–7.39 (m, 2 H), 13.40 (br s, 1 H).

¹³C NMR (125 MHz, CDCl₃): δ = 46.7, 66.1, 89.8, 107.6, 126.4, 129.9, 131.8, 135.8, 139.4, 146.9, 148.2, 155.7.

MS (EI, 70 eV): m/z (%) = 351 (100), 334 (37), 320 (27), 262 (46).

HRMS (EI): m/z calcd for $C_{16}H_{15}N_3O_2^{35}Cl_2$: 351.0541; found: 351.0536.

3-Chloro-*N*-(4-chlorophenyl)-5-methoxy-2-nitrosoaniline (2l)

Brown solid; yield: 115 mg (78%); mp 131–132 °C.

¹H NMR (500 MHz, CDCl₃): δ = 3.78 (s, 3 H), 6.20 (d, J = 2.5 Hz, 1 H), 6.71 (d, J = 2.5 Hz, 1 H), 7.17–7.21 (m, 2 H), 7.39–7.42 (m, 2 H), 13.40 (br s, 1 H).

¹³C NMR (125 MHz, CDCl₃): δ = 56.2, 93.0, 110.5, 126.6, 130.0, 132.5, 135.1, 138.3, 146.9, 149.7, 167.1.

MS (EI, 70 eV): m/z (%) = 296 (73), 279 (100), 265 (30), 231 (24).
HRMS (EI): m/z calcd for $C_{13}H_{10}N_2O_2^{35}Cl_2$: 296.0119; found: 296.0120.

5-Methoxy-2-nitroso-*N*-phenylaniline (2m)

Chromatography eluent: hexane–toluene, 1:1.

Green solid; yield: 60 mg (53%); mp 66–68 °C.

1H NMR (500 MHz, $CDCl_3$): δ = 3.79 (s, 3 H), 6.41 (br s, 1 H), 6.57–6.62 (m, 1 H), 7.26–7.29 (m, 3 H), 7.40–7.44 (m, 2 H), 8.56 (d, J = 8.7 Hz, 1 H), 12.93 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.9, 93.7, 109.5, 124.8, 126.5, 129.7, 136.9, 137.4, 142.6, 153.6, 167.2.

MS (EI, 70 eV): m/z (%) = 228 (26), 211 (100).

HRMS (EI): m/z calcd for $C_{13}H_{12}N_2O_2$: 228.0899; found: 228.0889.

3,5-Dimethoxy-2-nitroso-*N*-phenylaniline (2n)

Dark solid; yield: 123 mg (96%); mp 126–128 °C.

1H NMR (500 MHz, $DMSO-d_6$): δ = 3.80 (s, 3 H), 4.01 (s, 3 H), 6.02 (d, J = 2.3 Hz, 1 H), 6.12 (d, J = 2.3 Hz, 1 H), 7.27–7.30 (m, 1 H), 7.36–7.39 (m, 2 H), 7.43–7.48 (m, 2 H), 13.61 (br s, 1 H).

^{13}C NMR (125 MHz, $DMSO-d_6$): δ = 56.1, 56.5, 88.1, 90.2, 124.6, 126.2, 129.7, 136.7, 137.2, 146.8, 164.3, 169.5.

MS (EI, 70 eV): m/z (%) = 258 (100), 241 (73), 227 (41), 198 (23).

HRMS (EI): m/z calcd for $C_{14}H_{14}N_2O_3$: 258.1004; found: 258.1015.

2-{3-[(4-Fluorophenyl)amino]-4-nitrosophenoxy}ethan-1-ol (2o)

Dark green solid; yield: 119 mg (86%); mp 120–121 °C.

1H NMR (500 MHz, $CDCl_3$): δ = 3.95 (t, J = 4.6 Hz, 2 H), 4.06 (t, J = 4.6 Hz, 2 H), 6.26 (br s, 1 H), 6.64 (d, J = 8.2 Hz, 1 H), 7.09–7.16 (m, 2 H), 7.19–7.26 (m, 2 H), 8.60 (d, J = 8.2 Hz, 1 H), 12.69 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 60.9, 69.9, 94.6, 109.0, 116.7 (d, J_{C-F} = 23 Hz), 127.1 (d, J_{C-F} = 8.6 Hz), 132.7, 137.4, 143.1, 153.8, 161.0 (d, J_{C-F} = 246.1 Hz), 166.2.

MS (EI, 70 eV): m/z (%) = 276 (100), 262 (64), 259 (59).

HRMS (EI): m/z calcd for $C_{14}H_{13}N_2O_3F$: 276.0910; found: 276.0916.

*N*³-(4-Fluorophenyl)-4-nitroso-*N*¹-(prop-2-en-1-yl)benzene-1,3-diamine (2p)

Dark red solid; yield: 103 mg (76%); mp 115–116 °C.

1H NMR (500 MHz, $CDCl_3$): δ = 3.76–3.82 (m, 2 H), 5.17–5.26 (m, 2 H), 5.38–5.44 (m, 1 H), 5.78–5.88 (m, 2 H), 6.30 (dd, J = 9.2, 2.3 Hz, 1 H), 7.04–7.11 (m, 2 H), 7.19–7.24 (m, 2 H), 8.11 (d, J = 9.2 Hz, 1 H), 13.25 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 45.7, 88.5, 109.2, 116.3 (d, J_{C-F} = 22.4 Hz), 117.8, 126.8 (d, J_{C-F} = 8.3 Hz), 133.0, 133.5, 140.2, 141.7, 152.2, 155.4, 160.5 (d, J_{C-F} = 247.1 Hz).

MS (EI, 70 eV): m/z (%) = 271 (100), 257 (72), 199 (58), 216 (41).

HRMS (EI): m/z calcd for $C_{15}H_{14}N_3OF$: 271.1121; found: 271.1117.

N-(4-Ethoxyphenyl)-3-methoxy-2-nitroso-5-(pyrrolidin-1-yl)aniline (2q)

Chromatography eluent: acetone.

Dark red solid; yield: 153 mg (90%); mp 168–169 °C.

1H NMR (500 MHz, $CDCl_3$): δ = 1.43 (t, J = 7.0 Hz, 3 H), 1.90–2.04 (m, 4 H), 3.2–3.7 (m, 4 H), 4.01 (s, 3 H), 4.03 (q, J = 7.0 Hz, 2 H), 5.42 (d, J = 2.1 Hz, 1 H), 5.56 (d, J = 2.1 Hz, 1 H), 6.86–6.90 (m, 2 H), 7.15–7.18 (m, 2 H), 13.84 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.8, 25.1, 48.2, 56.0, 63.6, 83.0, 86.7, 115.1, 126.4, 130.7, 141.8, 145.2, 155.5, 156.7, 163.6.

MS (EI, 70 eV): m/z (%) = 341 (20), 327 (100), 323 (14).

HRMS (EI): m/z calcd for $C_{19}H_{23}N_3O_3$: 341.1739; found: 341.1735.

N-(4-Ethoxyphenyl)-3,5-dimethoxy-2-nitrosoaniline (2r)

Brown solid; yield: 122 mg (81%); mp 165–167 °C.

1H NMR (500 MHz, $CDCl_3$): δ = 1.43 (t, J = 7.0 Hz, 3 H), 3.73 (s, 3 H), 4.05 (q, J = 7.0 Hz, 2 H), 4.05 (s, 3 H), 5.83 (AB, J = 2.4 Hz, 2 H), 6.90–6.94 (m, 2 H), 7.13–7.17 (m, 2 H), 13.97 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.8, 55.8, 56.4, 63.7, 85.8, 89.8, 115.3, 126.7, 129.3, 140.4, 147.0, 157.6, 164.3, 169.5.

MS (EI, 70 eV): m/z (%) = 302 (100), 285 (61), 257 (80), 242 (50).

HRMS (EI): m/z calcd for $C_{16}H_{18}N_2O_4$: 302.1267; found: 302.1262.

N-(2,6-Dimethylphenyl)-3-methoxy-2-nitrosoaniline (3)

Dark solid; yield: 84.5 mg (66%); mp 144–146 °C.

1H NMR (500 MHz, $CDCl_3$): δ = 2.08 (s, 6 H), 4.14 (s, 3 H), 5.85 (dd, J = 8.9, 0.8 Hz, 1 H), 6.28 (dd, J = 7.9, 0.8 Hz, 1 H), 7.11–7.19 (m, 3 H), 7.21–7.26 (m, 1 H), 12.85 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.1, 56.4, 97.4, 106.2, 127.8, 128.5, 133.9, 135.6, 135.8, 141.0, 150.2, 163.5.

MS (EI, 70 eV): m/z (%) = 256 (24), 241 (100), 225 (35), 210 (58).

HRMS (EI): m/z calcd for $C_{15}H_{16}N_2O_2$: 256.1212; found: 256.1213.

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Supporting Information for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synthesis>.

References

- (1) (a) Bunnet, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273. (b) Miller, J. *Aromatic Nucleophilic Substitution*; Elsevier: Amsterdam, **1968**. (c) Terrier, F. *Nucleophilic Aromatic Displacement: The Influence of the Nitro Group*; J. Wiley & Sons: New York, **1991**.
- (2) (a) Crampton, M. R.; Emokpae, T. A.; Isanbor, C. *Eur. J. Org. Chem.* **2007**, 1378. (b) Crampton, M. R.; Emokpae, T. A.; Isanbor, C. *J. Phys. Org. Chem.* **2006**, *19*, 75. (c) Mancini, P. M.; Fortunato, G. G.; Vottero, L. R. *J. Phys. Org. Chem.* **2004**, *17*, 138.
- (3) (a) Chupakhin, O. N.; Charushin, V. N.; van der Plas, H. C. *Nucleophilic Aromatic Substitution of Hydrogen*; Academic Press: San Diego, **1994**. (b) van der Plas, H. C. *Adv. Heterocycl. Chem.* **2004**, *86*, 1. (c) Gulevskaya, A. V.; Pozharskii, A. F. *Adv. Heterocycl. Chem.* **2007**, *93*, 57. (d) Charushin, V. N.; Chupakhin, O. N. *Mendeleev Commun.* **2007**, *17*, 249.
- (4) (a) Mąkosza, M.; Wojciechowski, K. *Chem. Rev.* **2004**, *104*, 2631. (b) Mąkosza, M. *Synthesis* **2011**, 2341. (c) Mąkosza, M. *Chem. Soc. Rev.* **2010**, *39*, 2855.
- (5) (a) Wróbel, Z.; Kwast, A. *Synlett* **2007**, 1525. (b) Wróbel, Z.; Kwast, A. *Synthesis* **2010**, 3865.
- (6) Kwast, A.; Stachowska, K.; Trawczyński, A.; Wróbel, Z. *Tetrahedron Lett.* **2011**, *52*, 6484.
- (7) Wróbel, Z.; Stachowska, K.; Grudzień, K.; Kwast, A. *Synlett* **2011**, 1439.

- (8) Gościak, A.; Królikiewicz, M.; Kwast, A.; Pawłowski, R.; Stachowska, K.; Turska, I.; Wróbel, Z. *Helv. Chim. Acta* **2012**, in press, DOI: 10.1002/hlca.201200304.
- (9) Wirth, S.; Wallek, A. U.; Zernickel, A.; Feil, F.; Sztiller-Sikorska, M.; Lesiak-Mieczkowska, K.; Bräuchle, Ch.; Lorenz, I.-P.; Czyż, M. *J. Inorg. Biochem.* **2010**, *104*, 774.
- (10) Lipilin, D. L.; Churakov, A. M.; Ioffe, S. L.; Strelenko, Y. A.; Tartakovsky, V. A. *Eur. J. Org. Chem.* **1999**, 29.
- (11) (a) Bolton, R.; Sandall, P. B. *J. Chem. Soc., Perkin Trans. 2* **1978**, 1288. (b) Burdon, J.; Thomas, D. F. *Tetrahedron* **1965**, *21*, 2389.
- (12) (a) Gornostaev, L. M.; Bocharova, E. A.; Geets, N. V. *Russ. J. Org. Chem.* **2006**, *42*, 1289. (b) Bocharova, E. A.; Gornostaev, L. M.; Gritsan, N. P.; Gurova, T. N. *Russ. J. Org. Chem.* **2010**, *46*, 1639. (c) Gornostaev, L. M.; Bocharova, E. A.; Dolgushina, L. V.; Bagryanskaya, I. Yu.; Gatilov, Yu. V. *Russ. J. Org. Chem.* **2010**, *46*, 693.
- (13) Zumman, P.; Shah, B. *Chem. Rev.* **1994**, *94*, 1621.
- (14) Małosza, M.; Ludwiczak, S. *J. Org. Chem.* **1984**, *49*, 4562.
- (15) Małosza, M.; Voskresensky, S.; Białecki, M.; Kwast, A. *Pol. J. Chem.* **1999**, *73*, 1969.
- (16) Małosza, M.; Kwast, E. *Tetrahedron* **1995**, *51*, 8339.
- (17) Due to low solubility of **2i** in other deuterated solvents, the spectra were recorded in DMSO-*d*₆. While a complex mixture of isomeric forms was observed in this solvent at room temperature, acceptable spectra could be obtained at 80 °C, although two ¹³C signals were not visible.