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Ultrasonically activated reduction of substituted nitrobenzenes to corresponding *N*-arylhydroxylamines

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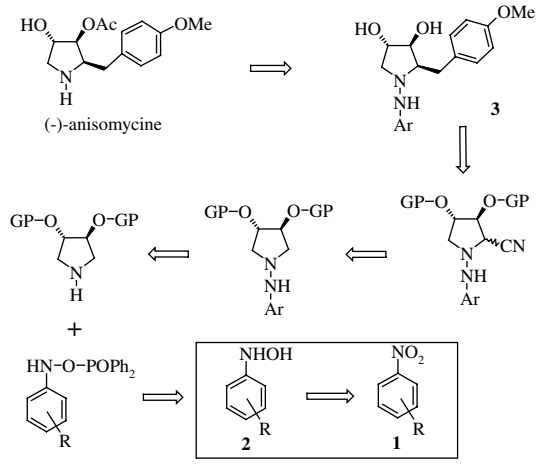
Abstract—Arylhydroxylamines can be obtained by reduction of the corresponding nitroaromatic compounds. We report here an efficient preparation of arylhydroxylamines by a controlled reduction of nitro compounds using zinc metal and ammonium chloride under ultrasonic activation in very short reaction times.

Nitroaromatics are major industrial products and well-known precursors of other valuable organic products. Indeed, the reduction of nitro compounds leads to various versatile classes of products such as amines, hydroxylamines, hydrazines, nitroso-, azo-, or azoxy compounds. The main difficulty is to control the selective access of only one of these products.

As part of an ongoing program involving a photoinduced single electron transfer (SET) reaction[1] to synthesize an antitumor substance, the (−)-anisomycin,[2] we were interested in the preparation of *N*-substituted arylhydrazines **3** as starting material via an umpolung strategy (Scheme 1).

Arylhydrazines **3** could be obtained by condensation of 3,4-disubstituted pyrrolidines with an *O*-activated derivative of the *N*-arylhydroxylamine **2** activated with diphenylphosphinyl chloride. This hydroxylamine **2** could result from the corresponding nitroaromatic compound **1** on condition that the reduction step is well controlled. It thus appeared that the conversion of nitrocompound to the corresponding arylhydroxylamine is the key step of our convergent planned synthetic route to (−)-anisomycin (Scheme 1).



Scheme 1.

As arylhydroxylamines are an important class of compounds frequently used as key intermediates in the synthesis of numerous fine chemicals,[3–5] we thus decided to study such a transformation. Several methods have been developed for the preparation of arylhydroxylamines; the more conventional one involves the reduction of nitroaromatic compounds to the corresponding *N*-hydroxylamines. Widely used is a reduction process involving a metal-mediated hydrogen transfer.[6] The procedure typically involves the use of a catalytic amount of an heavy metal (palladium, rhodium, iridium, or Raney nickel) together with hazardous reagents (metallic selenium or tellurium with sodium borohydride or bismuth

Keywords: Substituted nitrobenzenes; Reduction by zinc metal; Ultrasonication; Arylhydroxylamines; SET reactions.
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chloride with potassium borohydride).[7] Recently, Cui and co-workers have reported the reduction of nitroaromatic compounds to the corresponding hydroxylamines using baker's yeast or plant cells which represents the first example for preparation of arylhydroxylamines using a biological process.[8] The quantitative reduction of nitroarenes bearing electron-withdrawing groups has shown good selectivity (hydroxylamine vs amine: ratios >90:10); however the major drawback of this biological process is the large quantity of biocatalyst required (2.5–5.0 g per 100 mg of substrate).

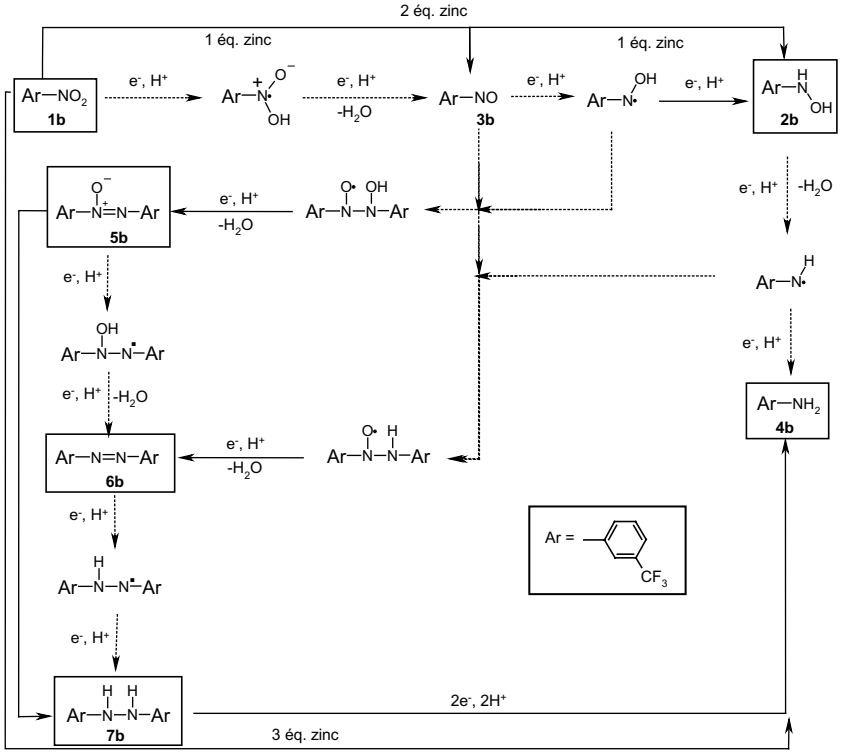
The reduction of the nitroaromatic compounds is also possible using zinc metal together with ammonium chloride in an aqueous suspension. First described by Kamm,[9] this procedure is frequently used but yields are not often mentioned due to the high reactivity of the resulting *N*-arylhydroxylamines that are generally engaged in the next step without isolation or further purification steps. The best results are obtained when the reaction occurs at 65–70 °C.

In order to improve this reduction procedure in terms of selectivity, generality and reaction time, we were interested in studying the effect of ultrasounds on the reaction. Indeed, the advantageous use of ultrasound irradiation technique for activating various reactions proceeding via electron transfer mechanism or radical route is well documented in the literature.[10] Solid–liquid heterogeneous reactions under ultrasound irradiation undergo pulverization of solid particles and simultaneous activation of surface.[11] As well as being energy efficient, ultrasounds can also enhance the rate of the reactions and, in many cases, improve product yields and sometimes can replace phase-transfer catalyst.

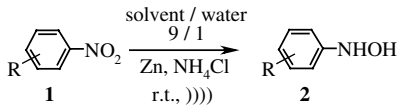
As depicted in Scheme 2,[12] a literature survey reveals that reduction of nitroaromatic compounds proceeds by SET mechanisms to form amines through intermediate stages involving hydroxylamines and nitroso compounds. *N*-Hydroxylamines are often reduced further to the corresponding amines. Moreover, amines and hydroxylamines generated in situ can react together and lead to the formation of azoxy- or azo-compounds.

We thus herein, report an effective conversion of nitroaromatic compounds to the corresponding *N*-arylhydroxylamines using 2 equiv of zinc dust (as proposed in Scheme 2) and ammonium chloride under ultrasonic activation. The easy experimental protocol together with the safety of the reagents implied encouraged us to choose this latter reductive method to prepare the target hydoxylamine **2**.

We decided to use the 4-hydroxyamino-benzoic acid ethylester **1a** as a model substrate in order to find optimal conditions. The conversion to the corresponding *N*-hydroxylamine **2a** was found to best proceed by using 2.1 M equiv of zinc in a 9:1 ethanol–water solvent mixture and in the presence of ammonium chloride (Scheme 3). In these conditions, we observed a dramatic effect of the ultrasonic activation, as the total conversion occurs within few minutes at room temperature (zinc dust was added by portions within a few minutes and the ultrasounds irradiation was halted 3–5 min after addition of the powder). Moreover, the crude *N*-hydroxylamine



Scheme 2.



Scheme 3.

2a was isolated in high yield (90%) with an NMR estimated degree of purity superior to 95% (Table 1, entry 1).

In order to avoid some difficulties in solubilizing other substrates, we then changed ethanol to acetone. Such a change improved the system as the crude hydroxylamine **2a** was obtained in a quantitative yield without any loss of purity (>95%). Various other substituted nitrobenzenes were then converted to *N*-arylhydroxylamines using this procedure (Table 1, entries 2–5). In all cases, the yields were good to excellent and the purity of the crude products always superior to 95%. Over-reduction to the corresponding anilines **5** was prevented by simple filtration of the zinc dust. However, long-term storage of the hydroxylamines is not advised since they are known to deteriorate over rather short periods of time.

Very good results were obtained with nitroaromatics bearing electron-withdrawing substituents. The reactions proceeded in about 5 min in almost quantitative yields. It is noteworthy that 4-hydroxyamino-benzoic acid ethylester **2a** and *m*-trifluoromethylphenyl-*N*-hydroxylamine **2b** were found to be stable under storage at room temperature.

The electron-donating substituted nitroaromatics such as *p*-methyl or *p*-methoxy were found to react as well in these conditions but led to unstable hydroxylamines that spontaneously were transformed in a mixture of over-reduced products. We have also observed a spontaneous conversion of 4-chlorophenyl-*N*-hydroxylamine **2f** (R = *p*-Cl) (obtained in 65% yield with 95% purity) to the corresponding azo derivative **7f** and 4-chloroaniline **5f** when zinc dust was not rapidly filtered. In such conditions, only 20% of 4-chlorophenyl-*N*-hydroxylamine **2f** had been recovered in less than 1 h.

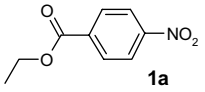
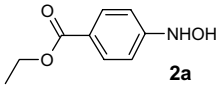
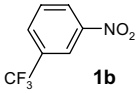
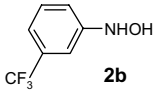
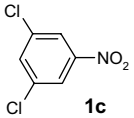
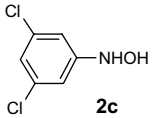
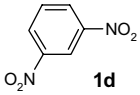
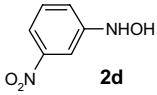
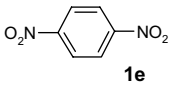
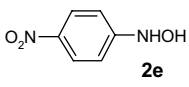
In the case of compound **1b**, we observed an interesting conjugated effect of the quantity of zinc dust, the nature of the medium and the time of ultrasonication on the course of the reaction. We have thus established four experimental protocols that selectively lead to one of the four reduction products, *N*-arylhydroxylamine **2b**, amine **5b**, azo **7b**, or hydrazine **8b** (Table 2).

Moreover, from 3,3′-trifluoromethylhydrazobenzene **8b** in HCl 3 N under ultrasonic conditions, we observed, after the cleavage of the hydrazo bond, the radical coupling with acetone providing *m*-trifluoromethyl-*N*-isopropylaniline **9** (Scheme 4).

As shown in Table 2, the results we have obtained by reduction with zinc under ultrasonication are consistent with mechanisms by SET proposed in the literature[12] (Scheme 2).

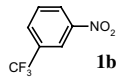
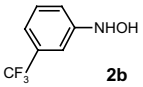
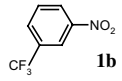
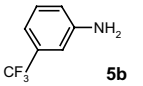
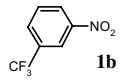
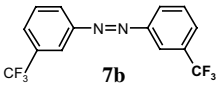
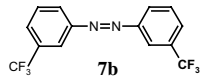
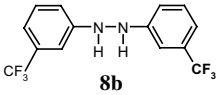
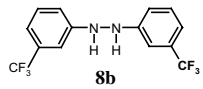
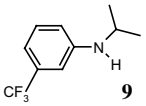
In summary, we reported here a study on the ultrasonic activation which can be a fast and powerful tool in selective nitroaromatics reduction reactions to corresponding *N*-arylhydroxylamines, avoiding the formation of over-reduced products. Because of its simplicity, high selectivity, short reaction times and high yields, this method can be used as a valid alternative to other reduction processes.

Table 1.

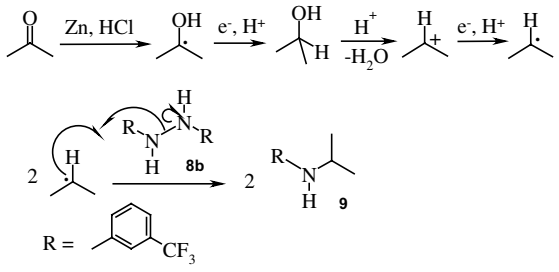
Entry	Substrate **1**	Solvent	Time (min)	Product **2**	Yield[a] (%)	Purity[b] (%)
1	 **1a**	Ethanol Acetone	5 5	 **2a**	90 100	>95 >95
2	 **1b**	Acetone	5	 **2b**	95	>95
3	 **1c**	Acetone	5	 **2c**	95	100
4	 **1d**	Acetone	5	 **2d**	75	>95
5	 **1e**	Acetone	5	 **2e**	85	100

[a] Crude products.
[b] Estimated by NMR analysis.[13]

Table 2.

Starting material	Zinc (equiv)	Solvent	Time[a,b]	Product	Yield[c] (%)	Purity[d] (%)
 **1b**	2.1	Acetone/H_2O	5 min	 **2b**	95	94.8
 **1b**	3.3	EtOH/HCl 3 N	10 min	 **5b**	100	96.2
 **1b**	2.1	Acetone/H_2O	3 days	 **7b**	20–30	99.4
 **7b**	1.2	Acetone/H_2O	<5 min	 **8b**	92	97.6
 **8b**	10	Acetone/HCl 3 N	30 min	 **9**	55	100

[a] All reactions were realized under ultrasonic activation.
[b] Reactions were monitored by analytical HPLC at 280 nm wavelength (ODS C18 column; acetonitrile–water 70:30; 1.4 mL/min flow rate).
[c] Crude yield.
[d] Estimated by HPLC.



Scheme 4.

As the reactions occur in less than 5 min at room temperature, this method is appropriate to highly functionalized nitrocompounds. Moreover, as zinc is inexpensive and non toxic, the use of this metal enhances the synthetic convenience and fulfills the demand for an environmentally friendly process.

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Vilarrasa, J. *Tetrahedron* **1990**, *46*, 587; (e) Bordwell, F. G.; Liu, W. *J. Am. Chem. Soc.* **1996**, *118*, 8777; (f) Heaney, F.; Rooney, O.; Cunningham, D.; McArdle, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, *2*, 373; (g) Beissel, T.; Powers, R. E.; Parac, T. N.; Raymond, K. N. *J. Am. Chem. Soc.* **1999**, *121*, 4200; (h) McGill, A. D.; Zhang, W.; Wittbrodt, J.; Wang, J.; Schlegel, B.; Wang, P. G. *Bioorg. Med. Chem.* **2000**, *8*, 405.

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13. *Typical procedure for substituted phenylhydroxylamines preparation:* To a suspension of nitrocompound **1** (3 mmol, 1 equiv) in acetone (40 mL) and saturated NH_4Cl aqueous solution (2 mL) was added distilled water (2–3 mL) until the solution became clear. Zinc dust (2.1 equiv) was added slowly by portions while sonicating (Transonic Elma ultrasonic bath, 35 kHz) the reaction mixture at 15–20 °C for few minutes (5–10 min). TLC monitoring of the reaction was done till the completion of the reaction. The crude mixture was concentrated under reduced pressure and a temperature never exceeding 15 °C. The residue obtained was dissolved in CH_2Cl_2 (20 mL) at 0 °C. The organic phase was dried over magnesium sulfate, then concentrated as above to provide the pure hydroxylamine **2** as a pale-yellow oil.

4-Hydroxyamino-benzoic acid ethylester **2a**: GC/MS: *m/z* (%): 166 (100), 165 (27), 120 (27). IR (KBr plate): 3388, 3292, 2973, 1686 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, 2H, $J = 9.2$ Hz, H-2), 6,98 (d, 2H, $J = 9.2$ Hz, H-3), 6.98 (s, 1H, OH), 5.58 (s, 1H, NH), 4.34 (q, 2H, $J = 7.2$ Hz), 1.39 (t, 3H, $J = 7.2$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7 (C=O), 153.9 (C-1), 130.9 (C-2), 123.4 (C-4), 112.9 (C-3), 60.7 (CH_2), 14.3 (CH_3).

N-(3-Trifluoromethylphenyl)-hydroxylamine **2b**: GC/MS: *m/z* (%): 177 (100) [M^+], 160 (97), 158 (18), 145 (48), 120 (15), 76 (3). IR (KBr plate): 3224, 3084, 2853 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (t, 1H, $J_{5,6} \approx J_{6,7} \approx 8.0$ Hz), 7.25 (s, 1H), 7.21 (d, 1H, $J = 7.7$ Hz, H-4), 7.11 (d, 1H, $J = 8.2$ Hz, H-6), 6.88 (s, 1H, OH), 5.49 (s, 1H, NH).

N-(3,5-Dichlorophenyl)-hydroxylamine **2c**: GC/MS: *m/z* (%): 178 (7) [M^+], 161 (100), 145 (13), 125 (22), 90 (22), 75 (13). IR (KBr plate): 3430, 3280, 3087, 2863 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.92 (s, 1H), 6.87 (s, 2H), 6.79 (s, 1H, OH), 5.23 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.6 (C-3), 135.4 (C-5), 121.9 (C-1), 112.6 (C-2).

N-(3-Nitrophenyl)-hydroxylamine **2d**: IR (KBr plate): 3288, 3196, 3068 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.88 (s, 1H, OH), 8.77 (s, 1H, NH), 7.61 (s, 1H), 7.56 (d, 1H, $J = 8.1$ Hz, H-4), 7.42 (t, 1H, $J_{6,7} = J_{5,6} = 8.1$ Hz), 7.19 (d, 1H, $J = 8.1$ Hz, H-6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 153.1 (C-3), 148.3 (C-4), 129.5 (C-2), 118.7 (C-1), 113.2 (C-6), 106.1 (C-5).

N-(4-nitrophenyl)-hydroxylamine **2e**: IR (KBr plate): 3355, 3306, 3070, 3030 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 9.64 (s, 1H, OH), 9.10 (s, 1H, NH), 8.07 (d, 2H, $J = 9.4$ Hz, H-3), 6.80 (d, 2H, $J = 9.4$ Hz, H-2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.6 (C-4), 137.5 (C-3), 125.5 (C-1), 109.8 (C-2).

N-(4-Chlorophenyl)-hydroxylamine **2f**: ^1H NMR (400 MHz, $CDCl_3$): δ 7.17 (d, 2H, $J = 8.8$ Hz, H-3), 7.16 (s, 1H, OH), 6.83 (d, 2H, $J = 8.8$ Hz, H-2), 6.76 (s, 1H, NH).