A Practical and Chemoselective Reduction of Nitroarenes to Anilines Using Activated Iron

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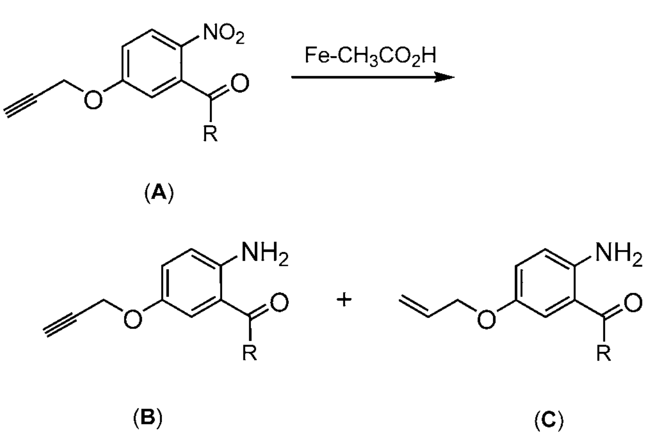
Abstract: Reduction of nitroarenes to anilines using activated iron generated by Fe/HCl or Zn/$FeSO_4$ is described. A variety of functional groups such as alkyne, ketone, enone, nitrile, lactone, and aromatic halide are well tolerated under these conditions.

Keywords: anilines, chemoselectivity, iron, nitroarenes, reduction, zinc

Numerous methods have been reported in the literature for the reduction of nitroarenes to anilines.[1] The most commonly used methods utilize iron,[2] such as Fe-NH_4Cl, Fe-AcOH, Fe-HCl, Fe-$CaCl_2$, $FeCl_3$-Zn-DMF-H_2O, FeS-NH_4Cl-CH_3OH-H_2O, etc., and zinc,[3] such as Zn-AcOH, Zn-NaOH, Zn-NH_4Cl, Zn-$CaCl_2$, etc. Less commonly used are methods utilizing indium-ultrasound[4] and indium-dichlorotitanocene.[5] Reductions using catalytic hydrogenation are also well known.[6] Selective methods for the reduction of the nitro group in the presence of other reducible functional groups are highly desirable. In a development program, we needed to find an efficient method for the reduction of an aromatic nitro group in (**A**) to the corresponding aniline (**B**) that would tolerate an aromatic ketone and a propargyl functional group and that was suitable for a large scale process in the pilot plant.



We elected to use iron as the reducing agent because it is cheap and readily available, and known to tolerate a variety of functionalities. Furthermore, palladium catalyst-based conditions often afford difficult to remove residues. To our disappointment, reduction of (**A**) using Fe-AcOH was slow, gave poor conversion (37%) and produced several by-products, one of which (**C**, 7%) resulted from reduction of both the nitro group and the propargyl group. This by-product was difficult to remove by either silica gel chromatography or by crystallization of a variety of salts. We next studied this reduction using Fe-NH_4Cl. However, the reduction was incomplete even at reflux in ethanol. One interesting observation was that the conversion of the starting material was not consistent from run to run, and only in one case when additional NH_4Cl was added after the reaction mixture was heated at reflux for 16 h, was a complete conversion observed. However, we were unable to reproduce these results. We reasoned that although prolonged heating of the substrate with Fe-NH_4Cl did not improve the conversion, the surface of the iron might have been altered (perhaps cleaned) with prolonged heating, thereby activating the iron, and the addition of more NH_4Cl triggered complete reduction of the substrate. If this hypothesis was correct, then pretreatment of iron using a stronger acid such as HCl might activate the iron surface more efficiently, and the reaction could be made reproducible. Thus, a suspension of iron powder (5.0 equivs.) in ethanol was heated with *concentrated* HCl (0.5 equivs.) at 65 °C for 2 h, and the mixture was cooled to 55 °C. A solution of NH_4Cl solution was added, followed by the addition of the nitroarene (1.0 equiv.) in portions. The reaction was exothermic and was complete in 1–3 h. The corresponding aniline product was obtained in excellent yield with $<1.0\%$ of the allyl by-product. Normally, NH_4Cl solution was necessary for the reaction to go to completion, however, for reactive substrates such as 2-bromo-5-chloro-nitrobenzene, the reduction proceeded smoothly to completion even without the use of NH_4Cl. Because concentrated HCl was consumed during the initial activation stage, the reaction medium was virtually neutral, which was in contrast to those methods involving Fe/HCl where acid-sensitive functional groups did not survive. By sim-

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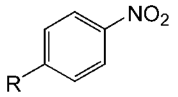
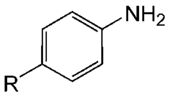
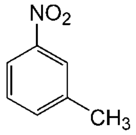
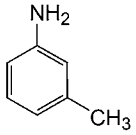
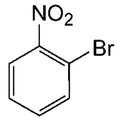
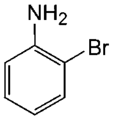
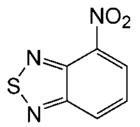
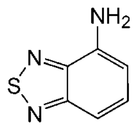
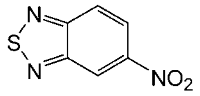
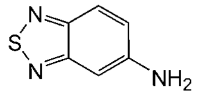
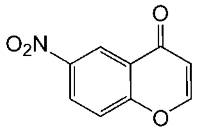
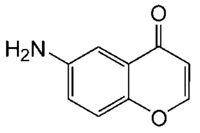
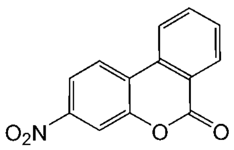
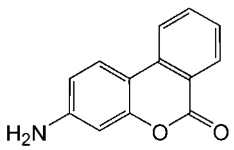
Table 1. Reduction of nitroarenes to anilines.

Substrate	Product	Yield [%]	
		Method A	Method B
			
1a R = $-CH_2CN$	**2a** R = $-CH_2CN$	87	81
1b R = -CN	**2b** R = -CN	99	88
1c R = -COPh	**2c** R = -COPh	98	98
1d R = -Cl	**2d** R = -Cl	99	93
1e R = $-OCH_2-C\equiv CH$	**2e** R = $-OCH_2-C\equiv CH$	91	86
 **1f**	 **2f**	90	80
 **1g**	 **2g**	90	87
 **1h**	 **2h**	90	95
 **1i**	 **2i**	88	95
 **1j**	 **2j**	73	70
 **1k**	 **2k**	85	88

ply activating iron *in situ* with concentrated HCl, we have discovered a convenient, highly chemoselective and reproducible reduction of nitroarenes to the corresponding anilines. Interestingly, other acids such as AcOH, H_2SO_4 and H_3PO_4 did not provide the same effect as HCl.

To further test the idea that an activated form of iron was indeed operational in the reduction of nitroarenes to the corresponding anilines, we generated an activated form of iron in another way by treating ferrous sulfate with zinc powder in the presence of NH_4Cl solution in ethanol. We found that the reduction worked very well, and similar results were obtained under these conditions. The results obtained using both methods are summarized in Table 1. An examination of Table 1 suggested that a variety of functional groups were well tolerated under these conditions.[7]

In conclusion, reduction of nitroarenes to anilines using activated iron generated by Fe/HCl or Zn/$FeSO_4$ is described. A variety of functional groups such as alkyne, ketone, enone, nitrile, lactone, and aromatic halide are well tolerated under these conditions.

Experimental Section

All the compounds gave satisfactory spectral and analytical data. Compounds **2a–d**, **2f–i** are cataloged chemicals. Compounds **2e**, **2j**, and **2k** are known in the literature.[8]

General Procedure (Method A)

A 250-mL, 3-necked, round-bottomed flask was charged with ethanol (80 mL). Iron powder (250 mmol, < 10 µm) was added in portions under efficient stirring, followed by concentrated HCl (25 mmol). The suspension was stirred at 65 °C for 2 h and was then cooled to 55–60 °C over a period of 10 min. Then 25% aqueous ammonium chloride solution (40 mL) was added. The nitroarene (50 mmol) was added in portions (exothermic) over a period of 30 min while maintaining the internal temperature at 65–80 °C. The reaction mixture was stirred at 55–65 °C for an additional 1–3 h and was cooled to 40 °C. Ethanol (100 mL) and Celite (20 g) were added subsequently. The reaction mixture was filtered over a pad of Celite (15 g) with suction. The filter cake was washed with EtOH (100 mL), and the filtrate was concentrated under reduced pressure to give a residue. To the residue, isopropyl acetate (120 mL) and saturated $NaHCO_3$ (50 mL) were added. The biphasic mixture was stirred at 20–25 °C, and the organic layer was separated. The organic layer was washed with brine (1 × 30 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure to afford the crude product. The purity of the crude product was usually > 97%.

General Procedure (Method B)

A 100-mL, 3-necked flask was charged with a nitroarene (10 mmol) and ethanol (50 mL). Iron sulfate heptahydrate (30 mmol), water (9 mL) and ammonium chloride (80 mmol) were added subsequently with efficient stirring. Then zinc powder (30 mmol, < 10 µm) was added to the reaction mixture. The reaction was exothermic and the internal temperature rose to 30–35 °C in ~3 min. The reaction mixture was heated to an internal temperature of 50 °C and stirred for an additional 1–3 h. It was then cooled to room temperature and filtered over a pad of Celite (5 g) with suction. The filter cake was washed with EtOH (70 mL), and the filtrate was concentrated under reduced pressure to give a residue. To the residue, isopropyl acetate (70 mL) and 25% aqueous ammonium chloride (30 mL) solution were added. The biphasic mixture was stirred at room temperature for 5 min and the organic layer was separated. The organic layer was washed with water (30 mL), saturated $NaHCO_3$ (30 mL), and brine (30 mL), and dried over sodium sulfate. The solvents were removed under reduced pressure to afford the crude product. The purity of the crude product was usually > 97%.

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[7] Intermediates such as nitrosoarenes have been observed (ref.[2i]), but we did not observe these intermediates probably because they were more reactive than the corresponding nitroarenes under our reaction conditions.

[8] Compound **2e**: F. K. Kurbanov, K. D. Allaberganov, A. B. Kuchkarov, *Izvestiya Vysshikh Uchebnykh Zavedenii, Khimiya I Khimicheskaya Tekhnologiya* **1976**, *19*, 653; compound **2j**: P. P. Joshi, T. R. Ingle, B. V. Bhide, *J. Indian Chem. Soc.* **1960**, *37*, 479; compound **2k**: Z. Lin, C. M. Tegley, E. A. Kallel, K. B. Marschke, D. E. Mais, M. Gottardis, T. K. Jones, *J. Med. Chem.* **1998**, *41*, 291.