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EFFICIENT REDUCING SYSTEM BASED ON IRON FOR CONVERSION OF NITROARENES TO ANILINES

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Reduction of nitroarenes with low solubility in $EtOH-H_2O$ to anilines easily occurs in a $Fe-NH_4Cl$ -acetone- H_2O system, and treatment of the same nitroarenes with $Fe-NH_4Cl$ - $EtOH-H_2O$ hardly furnished the corresponding products. Under the reaction condition, the reducible or hydrolysable groups are not affected.

Keywords: Aniline; Fe-NH₄Cl-acetone-H₂O; nitroarene; reduction

Aromatic amines are versatile synthetic intermediates in the preparation of important chemicals such as dyes and pharmaceutical chemicals. Numerous methods have been reported in the literature for the reduction of nitroarenes to anilines.^[1] Many reductive agents have been recommended for this transformation, and the most commonly used methods utilize iron,^[2,3] such as Fe–AcOH, and zinc,^[4,5] such as Zn–HCl and Zn–NH₄Cl. In comparison with other reducing reagents, Fe–NH₄Cl is a mild, neutral, and selective reducing system and finds wide application in organic synthesis because of its ready availability, ease of handling, and low cost.

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 aromatic nitro compounds bearing halogen or cyano groups to the corresponding anilines.^[6,7] When reduction of nitro compound **1** (Fig. 1) was run in water by using Zn–HCl, we found that a bromide was reduced simultaneously. We next studied this reduction using Fe–NH₄Cl in H₂O–EtOH or H₂O–MeOH, which is a typical procedure for reduction of aromatic nitro compounds.^[8,9] However, the reduction was incomplete even at reflux for a day because of the poor solubility of compound **1**. One interesting observation was that the conversion of the starting material was not consistent from run to run. This promoted us to study the effect of acetone, and we realized better yields without affecting bromides. To widen the synthetic utility of the reagent and conditions, many nitro aryls are tested. The high yields of the reduction products demonstrate the efficiency of this new method.

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Figure 1. The chemical structure of compound 1.

RESULTS AND DISCUSSION

We herein report a mild, neutral, efficient, and selective reducing system, $Fe-NH_4Cl$ -acetone, to convert nitroarenes to anilines (Scheme 1). This system is especially suitable for conversion of an aromatic nitro compound with poor solubility in ethanol (EtOH) to the corresponding amine. For the first try, we worried that the resulting aniline would condense with acetone to form a Schiff base in situ. Fortunately, this was not a problem, and the desired product was obtained in good to high yield. Tetrahydrofuran is also a suitable solvent except for acetone. To investigate how wide the ranges of structural variations in reactant molecules could be tolerated by the reaction, eight substituents (Br, OH, OMe, OBn, CO_2Et , CH_2CN , PhSO₃, and CH_2CO_2Et) were used. These substituents were selected primarily for their wide range of electronic and reducible properties. The results are summarized in Table 1. The functional group tolerance of this method is evident from entries 1–11,

Table 1. Reduction of aromatic nitro compounds by Fe-NH₄Cl in water-acetone



Entry	\mathbb{R}^1	\mathbb{R}^2	\mathbb{R}^3	\mathbb{R}^4	Mp (°C)	Ref.	Yield (%)
1	Н	F	Н		Liquid	186–187/760 torr ^[10]	79
2	Н	CO ₂ Me	Н		112–113	111-112 ^[11]	87
3	Н	CH ₂ CN	Н		48-49	47-49 ^[12]	91
4	Н	CH ₂ CO ₂ Me	Н		Liquid	240-250/17 torr ^[13]	85
5	CH ₂ CO ₂ Me	H	Н	OH	81-83		86
6	CH ₂ CO ₂ Me	Н	Н	OMe	Liquid	151–152/1 torr ^[14]	94
7	PhSO ₃	OH	PhSO ₃		155-157	New	80
8	PhSO ₃	OMe	$PhSO_3$		154-156	New	92
9	Br	OH	Br		191–193	191.5-192.5	85
10	Br	OMe	Br		65-67	66	67
11	Br	OBn	Br		106-107	_	98
12	Н	OMe	Н		62-63	61-62 ^[15]	90
13	Н	OBn	Н		53–54	54-55 ^[16]	93



Scheme 1. Schematic diagram showing the transformation of aromatic nitro compounds anilines in acetone (THF)-water solvent system.

which show that halogen, hydroxy, methoxy, sulfonate, ester, and cyano groups are unaffected under the reaction conditions. In particular, haloaromatic nitro compounds showed remarkable selectivity to give the anilines without any further dehalogenation.

A solid product is easy to crystallize from AcOEt–petroleum ether. As for a liquid product, the crude aniline is dissolved in hydrochloric acid (15%, v/v). After washing with AcOEt, the acid layer is alkalized with NaOH and extracted with AcOEt. The organic layer is subsequently neutralized and dried. A product with high purity is given after removal of solvent.

In conclusion, we have developed a simple and general procedure to convert an aromatic nitro compound to the corresponding amine. This method is especially suitable for reducing the aromatic nitro compounds with poor solubility in EtOH. Reducible functional groups such as halogen and CN as well as hydrolyzable groups such as ester and suffonate groups are unaffected under the reaction conditions.

EXPERIMENTAL

All chemicals (reagent grade) used were purchased from Aldrich (USA) and Sinopharm Chemical Reagent Co., Ltd. (China). Melting points (uncorrected) were determined on an XT4 MP apparatus (Taike Corp., Beijing, China). Electron-impact (EI) mass spectra were obtained on a Waters GCT mass spectrometer, and ¹H NMR spectra were recorded on a Bruker AV-500 spectrometer at 25°C with tetramethylsilane (TMS) and solvent signals allotted as internal standards. Chemical shifts were reported in parts per million (δ). Elemental analyses were performed on a CHN-O-Rapid instrument and were within $\pm 0.4\%$ of the theoretical values.

General Procedure for Reduction

Reduced iron powder was added was added to a solution of ammonium chloride (15 mmol) in water (10 mL) under a nitrogen atmosphere. To this stirring mixture, a solution of nitrocompound (5 mmol) in acetone (25 mL) was added dropwise. It was refluxed in an oil bath for 2-5 h (TLC monitering; see Table 1). When the reaction was over, the result was extracted with AcOEt, and the combined organic layer was basified by adding a saturated solution of NaHCO₃. After the mixture was washed and dried, the solvent was removed under reduced pressure. The amino compound was further purified as mentioned previously.

Selected Data

5-Amino-2-hydroxy-1,3-phenylene dibenzenesulfonate (7). White powder. ¹H NMR (300 MHz, d_6 -DMSO): 5.09 (bs, 2H), 6.33 (s, 2H), 7.63 (t, J = 7.5 Hz, 4H), 7.79 (t, J = 7.3 Hz, 2H), 7.82 (d, J = 7.5 Hz, 4H), 8.61 (s, 1H); EIMS m/z 421 (M⁺). Anal. calcd. for C₁₈H₁₅NO₇S₂: C, 51.30; H, 3.59; N, 3.32; S, 15.22. Found: C, 51.37; H, 3.58; N, 3.31; S, 15.27.

5-Amino-2-methoxy-1,3-phenylene dibenzenesulfonate (8). White powder. ¹H NMR (300 MHz, d_6 -DMSO): 3.25 (s, 3H), 5.49 (bs, 2H), 6.33 (s, 2H), 7.68 (t, J = 8.0 Hz, 4H), 7.81 (t, J = 7.7 Hz, 2H), 7.85 (d, J = 8.1 Hz, 4H); EIMS m/z 435 (M⁺). Anal. calcd. for C₁₉H₁₇NO₇S₂: C, 52.40; H, 3.93; N, 3.22; S, 14.73. Found: C, 52.36; H, 3.92; N, 3.24; S, 14.76.

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REFERENCES

- Kabalka, G. W.; Varma, R. S. Reduction of nitro and nitroso compounds. In *Comprehensive Organic Synthesis*, 1st ed.; B. M. Trost, and I. Fleming (Eds.); Pergamon Press: Oxford, 1991; vol. 8, p. 363.
- Macleod, C.; McKiernan, G. J.; Guthrie, E. J.; Farrugia, L. J.; Hamprecht, D. W.; Macritchie, J.; Hartley, R. C. Synthesis of 2-substituted benzofurans and indoles using functionalized titanium benzylidene reagents on solid phase. J. Org. Chem. 2003, 68, 387–401.
- Ramadas, K.; Srinivasan, N. Iron-ammonium chloride—A convenient and inexpensive reductant. Synth. Commun. 1992, 22, 3189–3195.
- Edwards, J. P.; Zhi, L.; Pooley, C. L. F.; Tegley, C. M.; West, S. J.; Wang, M.-W.; Gottardis, M. M.; Pathirana, C.; Schrader, W. T.; Jones, T. K. Preparation, resolution, and biological evaluation of 5-aryl-1,2-dihydro-5H-chromeno[3,4-f]-quinolines: Potent, orally active, nonsteroidal progesterone receptor agonists. *J. Med. Chem.* 1998, 41, 2779–2785.
- Matthews, J. M.; Greco, M. N.; Hecker, L. R.; Hoekstra, W. J.; Andrade-Gordon, P.; de Garavilla, L.; Demarest, K. T.; Ericson, E.; Gunnet, J. W.; Hageman, W.; Look, R.; Moore, J. B.; Maryanoff, B. E. Synthesis and biological evaluation of novel indoloazepine derivatives as non-peptide vasopressin V2 receptor antagonists. *Bioorg. Med. Chem. Lett.* 2003, 13, 753–756.
- Xiao, Z. P.; Li, H. Q.; Shi, L.; Lv, P. C.; Song, Z. C.; Zhu, H. L. Synthesis, evaluation of antiproliferative activity and structure-activity relationship of 3-aryl-1H-quinolin-4-ones. *Chem. Med. Chem.* 2008, *3*, 1077–1083.
- Xiao, Z. P.; Lv, P. C.; Xu, S. P.; Zhu, T. T.; Zhu, H. L. Synthesis, antiproliferative evaluation and structure-activity relationship of 3-arylquinolines. *Chem. Med. Chem.* 2008, *3*, 1516–1519.

- Desai, D. G.; Swami, S. S.; Dabhade, S. K.; Ghagare, M. G. FeS-NH₄Cl-CH₃OH-H₂O: An efficient and inexpensive system for reduction of nitroarenes to anilines. *Synth. Commun.* 2001, *31*, 1249–1251.
- Zhu, J. L.; Wong, H.; Zhang, Z. G.; Yin, Z. W.; Meanwell, N. A.; Kadow, J. F.; Wang, T. An effective procedure for the preparation of 3-substituted-4- or 6-azaindoles from ortho-methyl nitro pyridines. *Tetrahedron Lett.* 2006, 47, 5653–5656.
- Patrick, T. B.; Schield, J. A.; Kirchner, D. G. Synthesis of fluoroaromatic amines. J. Org. Chem. 1974, 39, 1758–1761.
- Van de Graaf, B.; Hoefnagel, A. J.; Wepster, B. M. Substituent effects, 7: Microscopic dissociation constants of 4-amino- and 4-(dimethylamino)benzoic acid. J. Org. Chem. 1981, 46, 653–657.
- Srinivasa, G. R.; Abiraj, K.; Gowda, D. C. Clean and efficient hydrogenative cleavage of azo compounds using polymer-supported formate and zinc. *Synth. Commun.* 2005, 35, 1161–1166.
- Roberts, D. T.; Little, W. F.; Bursey, M. Ortho effect in the mass spectra of some carbonylsubstituted phenylferrocenes. J. Am. Chem. Soc. 1967, 89, 4917–4923.
- 14. Bersch, H. W. Zur Synthese der Homoisovanillinsäure. Arch. Pharm. 1939, 277, 271-286.
- Boyer, J.; Elizey, Jr., S. Notes—Reduction of the azido group with sodium borohydride. J. Org. Chem. 1958, 23, 127–129.
- Ward, R. S.; Cooks, R. G.; Williams, D. H. Substituent effects in mass spectrometry. Mass spectra of substituted phenyl benzyl ethers. J. Am. Chem. Soc. 1969, 91, 2727–2732.