JOC Note

Highly Chemoselective Reduction of Aromatic Nitro Compounds by Copper Nanoparticles/Ammonium Formate

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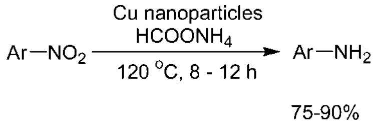
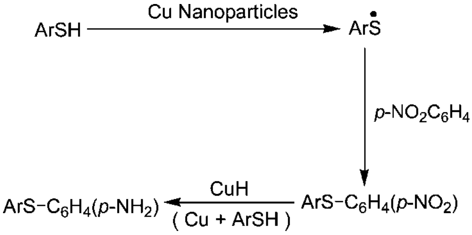


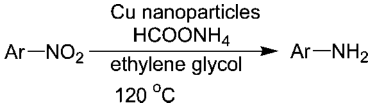
A highly chemoselective reduction of aromatic nitro compounds to the corresponding amino derivatives has been achieved by a combination of copper nanoparticles and ammonium formate in ethylene glycol at 120 °C. The reductions are successfully carried out in presence of a wide variety of other reducible functional groups in the molecule, such as Cl, I, OCH_2Ph, $NHCH_2Ph$, COR, COOR, CN, etc. The reactions are very clean and high yielding.

The use of metal nanoparticles for organic reactions has attracted tremendous interest in recent times.[1,2] As a part of our activities in this area we have demonstrated very efficient uses of palladium nanoparticles for the coupling of *vic*-diiodoalkenes with conjugated alkenes,[3a] Tsuji—Trost reaction,[3b] Hiyama coupling,[3c] and use of copper nanoparticles for aryl-sulfur bond formation.[3d] While carrying out the aryl-sulfur bond formation catalyzed by Cu nanoparticles (20 mol%), we observed an interesting reduction of the nitro group to an amino group in trace amount (5%) in the coupling of 4-nitroiodobenzene with 4-methylthiophenol (Scheme 1).[3d] We proposed that copper hydride (CuH), generated in situ during the reaction, as delineated in Scheme 1, was responsible for the reduction of NO_2 group. We then investigated the optimization of the reaction conditions using a stoichiometric amount of Cu nanoparticles and a convenient hydrogen source toward complete reduction of the NO_2 group. Ammonium formate was found to provide the best results in terms of yields and reaction time compared to other hydrogen sources such as hydrazine hydrate and H_2 gas. This led us to report here a novel protocol for the chemoselective reduction of aromatic nitro compounds by copper nanoparticles in combination with ammonium formate in ethylene glycol (Scheme 2).

SCHEME 1. Coupling of *p*-Nitroiodobenzene with Thiol Catalyzed by Cu Nanoparticles



SCHEME 2. Reduction of Aromatic Nitro Compound to Aniline



Aromatic amines are useful intermediates in the preparation of dyes, pharmaceuticals, and agricultural chemicals and can be easily obtained by the reduction of aromatic nitro compounds. A variety of procedures involving metals and other reducing agents are available for this purpose.[4] However, the selective reduction of a nitro group in the presence of other reducible functionalities in a molecule is a challenging task. In addition, reduction of aromatic nitro compounds often stops at an intermediate stage, producing hydroxylamines, hydrazines, and azoarenes as side products.[4b] Recently a few procedures involving coinage metal nanoparticles (Au, Ag, Cu/aqueous $NaBH_4$),[5a] gold nanoparticles supported on TiO_2 or Fe_2O_3/H_2,[5b] polymer-supported nanostructured platinum carbonyl cluster,[5c] and carbon nanofiber-supported platinum and palladium nanoparticles[5d] have been demonstrated for the reduction of nitro group. However, an alternative efficient, simple, chemoselective, and cost-effective procedure is highly appreciated.

The experimental procedure for our Cu nanoparticles-mediated reduction is very simple. A mixture of an aromatic nitro compound, Cu nanoparticles (size 4—6 nm as shown in Figure 1), and ammonium formate was heated at 120 °C in ethylene glycol. The product was obtained following a standard workup. A few other protic solvents such as methanol, ethanol, and water were also investigated; however, none of them gave satisfactory results.

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(2) (a) Ornelas, C.; Mery, D.; Blais, J. C.; Cloutet, E.; Aranzaes, J. R.; Astruc, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 7399–7404. (b) Astruc, D.; Lu, F.; Aranzaes, J. R. *Angew. Chem., Int. Ed.* **2005**, *44*, 7852–7872.

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10.1021/jo800863m CCC: $40.75

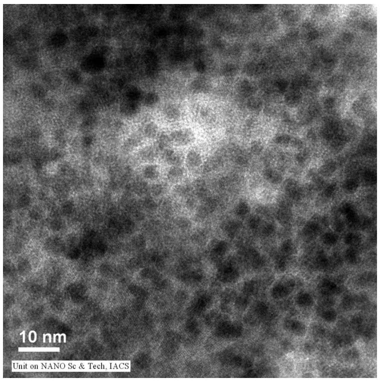

FIGURE 1. TEM image of Cu nanoparticles.

Several substituted aromatic nitro compounds were subjected to this procedure to produce the corresponding aromatic amines. The results are presented in Table 1. 4-Chloro- and 4-iodonitrobenzene (entries 5 and 6, Table 1) were cleanly reduced to the corresponding anilines without any dehalogenation, which was often encountered with several procedures such as hydrogenation.[4a,i] 6-Nitroquinoline (entry 7, Table 1) was reduced to 6-aminoquinoline keeping the heterocyclic ring intact. The *O*-benzyl, *N*-benzyl, ketocarbonyl, carboxylic ester, and nitrile functionalities present in the aromatic ring also remained unaffected during reduction of the corresponding nitrobenzenes by this procedure (entries 8−12, Table 1). *m*-Dinitrobenzene (entry 13, Table 1) was reduced selectively to *m*-nitroaniline. Many conventional procedures involving hydride reducing agents, hydrogenation, or indium failed to give such high chemoselectivity.[4] However, considerable reduction of the double bond conjugated to an aromatic ring was observed while reducing the nitro group (entry 14, Table 1). Similar reduction of the double bond in 4-allyloxy nitrobenzene was also found (entry 15, Table 1), although a completely isolated double bond, such as in 10-undecenoic ethyl ester, remained inert under the reaction conditions. In addition, the reactions with a vinylic nitro compound (*β*-nitrostyrene), 4-nitrobenzaldehyde, and 4-(*N*-benzylimino)-nitrobenzene were messy, giving a mixture of several unidentified compounds.

The reaction was not initiated at all using ammonium formate in the absence of Cu nanoparticles. The reaction was also not very effective with Cu nanoparticles without ammonium formate. Thus, a combination of Cu nanoparticles and ammonium formate is essential to carry out the reduction. Use of 5 equiv of ammonium formate led to complete conversion, and a lesser amount left the reaction incomplete. This might be due to fact that a portion of the ammonium formate, deposited by sublimation on the wall of the condenser with the progress of the reaction, remained unavailable for reaction, requiring a higher than stoichiometric amount. In general, all reductions are very clean and high yielding. No intermediate product was isolated in any reaction.

Copper nanoparticles were prepared from copper sulfate by reduction with hydrazine hydrate in ethylene glycol.[6] The identity of Cu nanoparticles was established by transmission electron microscopy (TEM) and energy dispersive X-ray spectroscopy (EDS) (Figure 1 and Figure 2).

TABLE 1. Reduction of Aromatic Nitro Compounds by Cu Nanoparticles/$HCOONH_4$[a]

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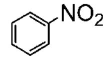
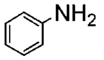
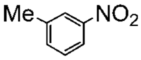
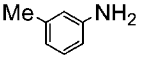
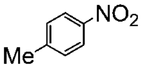
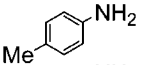
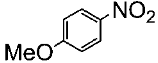
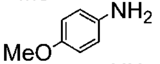
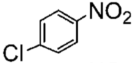
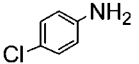
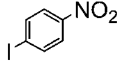
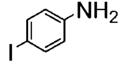
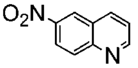
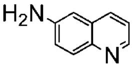
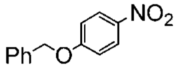
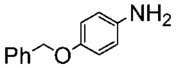
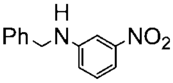
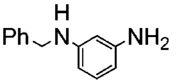
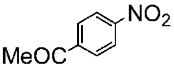
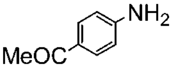
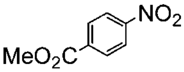
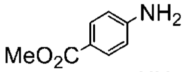
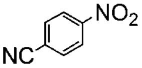
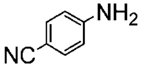
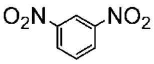
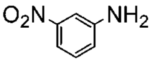
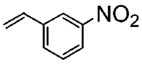
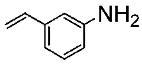
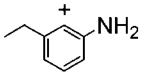
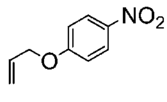
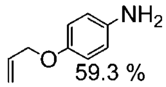
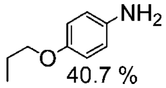
1		11		86	4g
2		12		80	4g
3		12		82	4g
4		12		83	4g
5		9		86	11
6		9		85	12
7		10		86	11
8		12		75	4f
9		9		77	13
10		8		90	4c
11		8		85	4d
12		9		86	4d
13		9		83	4c
14		12	 57.4 % +  42.6 %	73	5b
15		12	 59.3 % +  40.7 %	76	14

[a] Yields refer to those of purified products characterized by IR and ^1H and ^{13}C NMR spectroscopic data.

The TEM image showed the size of the nanoparticles to be in the range of 4−6 nm. These nanoparticles in ethylene glycol were used as such for the reaction. Possibly, ethylene glycol is providing stability to Cu nanoparticles.

The precise mechanism of this reduction process is not very clear to us. However, it is predicted that Cu nanoparticles form CuH by transfer hydrogenation from ammonium formate[7c] under the reaction conditions. Although efficient formation of CuH by reaction of Cu and H_2 needed high pressure,[7a] it is not unlikely that Cu nanoparticles because of low redox potential[5a] and superior reactivity readily form CuH in this procedure. As

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(6) Zhu, H.; Zhang, C.; Yim, Y. *Nanotechnology* **2005**, *16*, 3079–3083.

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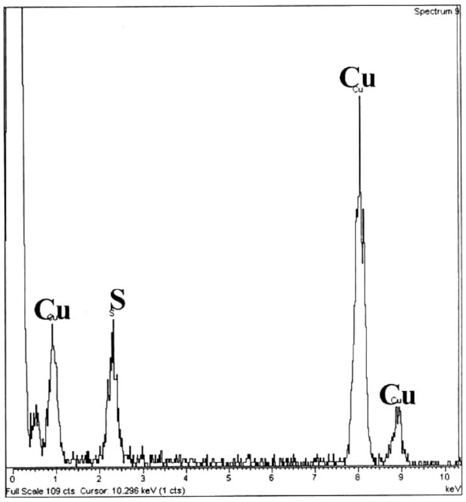
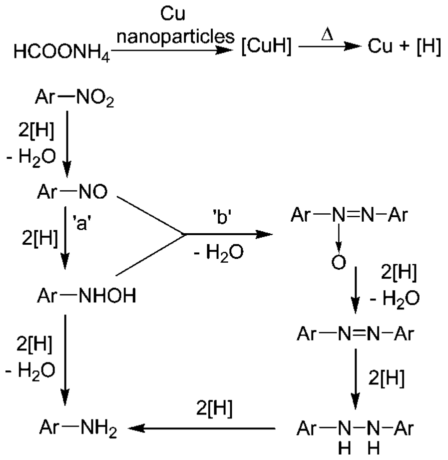


FIGURE 2. Energy dispersive X-ray spectra of Cu.

SCHEME 3. Proposed Reaction Pathway for Reduction of Aromatic Nitro Compounds by Cu Nanoparticles/HCOONH$_4$



CuH is thermally unstable[7b] it undergoes decomposition under the reaction conditions to generate Cu and hydrogen to effect reduction of nitro groups via a hydrogenation process.[8]

The reduction of aromatic nitro compounds may proceed by two different routes (Scheme 3).[9] In one, the nitro compound is first reduced to a nitroso compound which further proceeds to provide the hydroxylamine and finally gives rise to amine. In the second one, the initially formed nitroso compound may condense with hydroxylamine to produce the azoxy compound, which then may undergo further reduction to azo, hydrazo, and finally to amine. In order to find out the reaction pathway in the present reaction, we carried out a series of experiments with these intermediates. When nitrosobenzene and phenyl hydroxyl amine, obtained by different routes, were subjected to reduction by this procedure, aniline was obtained in 77% and 74% yields, respectively (Table 2). However, when azobenzene and hydrazobenzene, also obtained separately, were reduced under identical reaction conditions, aniline was formed only in 13% and 15% yields, respectively. These results clearly suggest that the azobenzene and hydroazobenzene route is disfavored and the nitroso and hydroxylamine one is the more probable pathway.

TABLE 2. Reduction of Nitrosobenzene, Phenyl Hydroxylamine, and Hydrazobenzene by Cu Nanoparticles/HCOONH$_4$

entry	substrate	time (h)	product	yield (%)[a]
1	Ph−NO	7	Ph-NH$_2$	77
2	Ph−NHOH	7	Ph-NH$_2$	74
3	Ph−N=N−Ph	12	Ph-NH$_2$	13
4	Ph−HN−NH−Ph	12	Ph-NH$_2$	15

[a] Yields refer to those of purified products characterized by IR and ^{1}H and ^{13}C NMR spectroscopic data.

TABLE 3. Comparison of Results of Reductions of Aromatic Nitro Compounds Using Metallic Cu Powder with Cu Nanoparticles[a]

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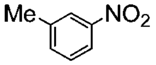
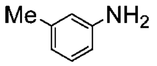
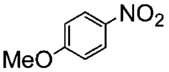
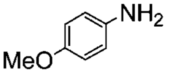
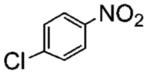
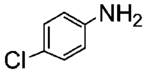
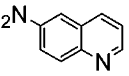
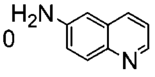
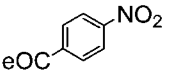
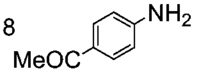
1		12		80	8
2		12		83	7
3		9		86	9
4		10		86	10
5		8		90	12

[a] Yields refer to those of purified products characterized by IR and ^{1}H and ^{13}C NMR spectroscopic data.

To check the efficiency of Cu nanoparticles for this reduction, a comparison of results of a few representative reactions by freshly prepared metallic Cu (prepared by the reaction of CuSO$_4$ and Zn dust[10]) is presented in Table 3. These results clearly demonstrated much higher efficiency of Cu nanoparticles compared to metallic Cu.

In conclusion, the present procedure using Cu nanoparticles and ammonium formate provides a very simple and efficient methodology for highly chemoselelective reductions of aromatic nitro compounds. The compatibility of such a wide spectra of reducible groups was not addressed earlier by other methods using noble metal nanoparticles,[5] and this certainly makes this procedure unique from others and very useful in organic synthesis. The cost effectiveness of Cu nanoparticles compared to other noble metals also adds to its advantage.

Experimental Section

Representative Experimental Procedure for Reduction of Aromatic Nitro Compound (entry 2, Table 1). A mixture of

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3-nitrotoluene (137 mg, 1 mmol), Cu nanoparticles (191 mg, 3 mmol) in ethylene glycol (10 mL), and ammonium formate (315 mg, 5 mmol) was heated at 120 °C with stirring for 12 h (TLC) under argon. Copper particles were filtered off through a short plug of silica gel. The filtrate was extracted with ethyl acetate. Evaporation of solvent followed by column chromatography over basic alumina furnished 3-nitroaniline (86 mg, 80%) as a pale yellow oil. The spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR) of this compound are in good agreement with those reported.[4g]

All of these products are known compounds (see refs in Table 1) and were easily characterized by comparison of their spectra with those reported.

This procedure is followed for all of the reactions listed in Table 1. Although the representative procedure is based on millimolar scale reaction, it has been scaled up to gram quantities with reproducible results.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of all the products listed in Table 1 and HRMS analysis of products in entries 5−12, 14, and 15 in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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