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Hydrogenation of Azides over Copper Nanoparticle Surface Using Ammonium Formate in Water

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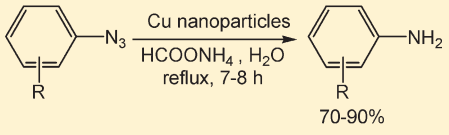
Ⓢ *Supporting Information*

ABSTRACT: Aryl azides undergo clean reduction by copper nanoparticles and ammonium formate in water. The surface hydrogen on copper nanoparticles is considered to be the active reducing species. A variety of functionalized aryl azides and aryl sulfonyl azides are reduced by this procedure to the corresponding amines with excellent chemoselectivity in high yields.



R = CH_3, OMe, F, Cl, Br, I, NO_2, CN, COOH, COMe, COOMe, N_3, *O*-Bn, *O*-Allyl, *N*-Bn, *N*-Allyl

The transition metal nanoparticles play an important role in organic reactions because of their high surface to volume ratio and larger number of active sites per unit area compared to the parent metal.[1] Hydrogenation over metals, particularly Pd and Pt, is widely used for the reduction of a variety of functionalities and is significantly influenced by the surface of the metal catalyst.[2] Recently, several reports appeared that demonstrated efficient hydrogenation over the surface of Pd, Pt, and Ru nanoparticles where these metals dissociate H_2 and facilitate the hydrogenation process.[3] However, although these noble metals are frequently employed, use of less expensive Cu nanoparticles for hydrogenation is very limited.[4] In general, copper metal and copper salts are more acceptable to the environment, and thus we became interested in finding new applications of Cu nanoparticles for hydrogenation of useful organo-functional groups with a particular attention to chemo-, regio-, and stereoselectivity.

Organic azides are very versatile and useful synthons and have wide applications in the synthesis of triazoles and other heterocycles.[5] The reduction of azides provides a very straightforward route to amines, which are an important class of compounds and have potential uses in chemistry and biology, such as synthesis of bioactive pharmaceuticals and natural products.[6] This protocol became more appealing because of the easy accessibility of azides from the corresponding halides and sulfonates.[7] A large variety of reducing agents have been employed for the conversion of azides to amines.[5c,8] These include a variety of hydride reducing agents,[5c] triphenyl phosphine,[8a] metal-catalyzed hydrogenations,[8b] radical initiators,[8c] $Zn(BH_4)_2$,[8d] Cl_2InH,[8e] molybdenum xanthate/$PhSiH_3$,[8f] etc. Although these reagents are, in general, satisfactory, several of them have limitations with regard to general applicability, cost efficiency, and selectivity, and their success also varies from substrate to substrate having other reducible functionalities.[9] Thus, an alternative, simple, and inexpensive reducing agent offering more eco-friendly reaction conditions and efficiency is appreciated. We report here a highly chemoselective reduction of aryl azides by hydrogenation on Cu(0) nanoparticle surfaces using ammonium formate in water (Scheme 1).

Scheme 1. Hydrogenation of Azides

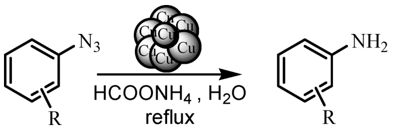
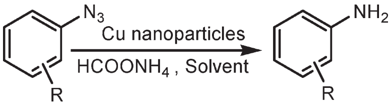


Table 1. Standardization of Reaction Conditions



entry	solvent	catalyst (Cu NPs)	temp (°C)	time (h)	yield (%)
1	THF	2 equiv	66	7	14
2	DMF	2 equiv	110	7	75
3	dioxane	2 equiv	100	7	31
4	toluene	2 equiv	100	7	24
5	H_2O	2 equiv	100	8	83
6	H_2O	2 equiv	70	8	10
7	H_2O	2 equiv	25	8	
8	H_2O	1 equiv	100	8	83
9	H_2O	0.5 equiv	100	8	83
10	H_2O	0.25 equiv	100	8	31

To standardize the reaction conditions, several experiments were performed for a representative reaction of phenyl azide with a varied amount of Cu nanoparticles with variation of solvent, reaction temperature, and time. The results are shown in Table 1. It was found that water at reflux for 8 h provides the best yield with 50 mol % of Cu nanoparticles (with respect to azide). Although the yield of product using DMF is comparable, those in relatively nonpolar THF, dioxane, and toluene are far from satisfactory. The reaction did not proceed at room temperature.

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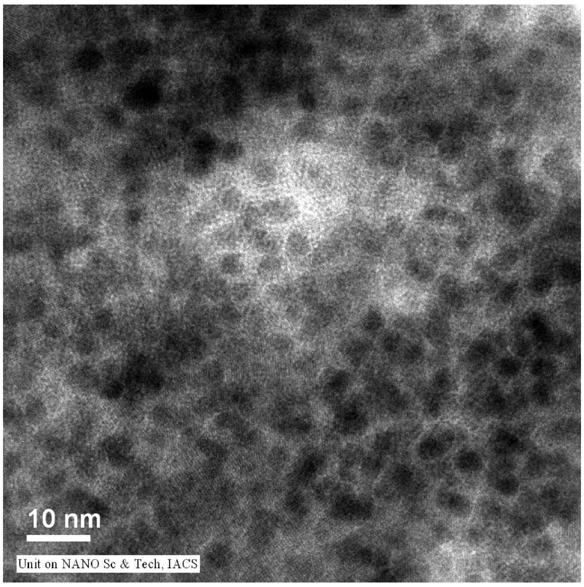


Figure 1. TEM image of Cu nanoparticles.

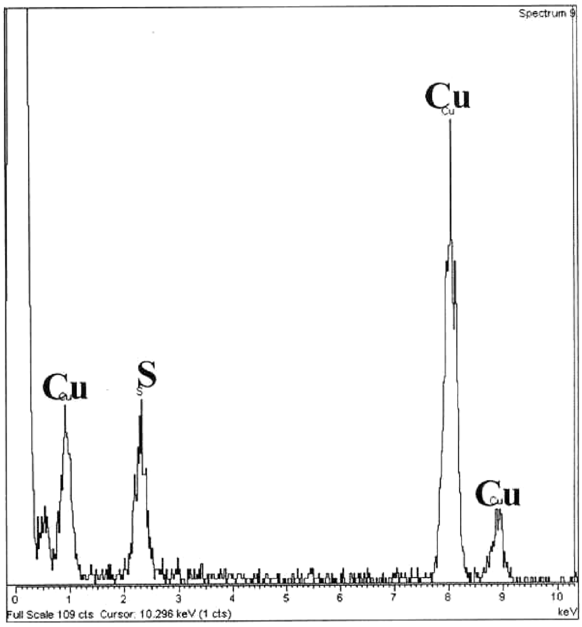
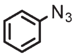
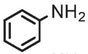
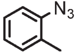
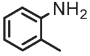
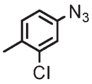
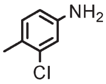
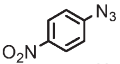
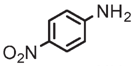
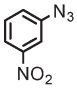
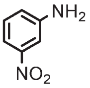
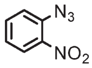
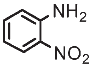
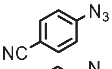
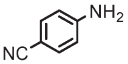
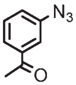
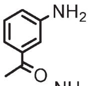
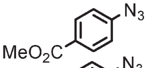
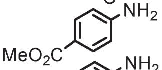
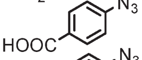
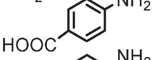
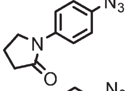
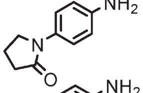
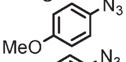
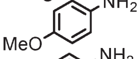
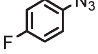
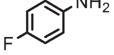
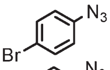
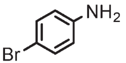
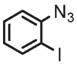
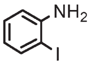
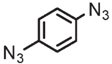
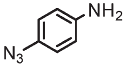
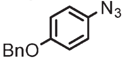
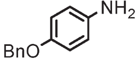
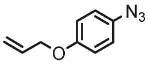
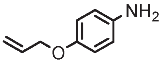
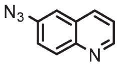
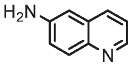
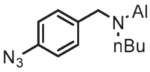
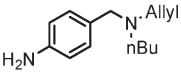
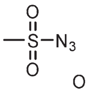
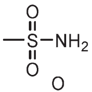
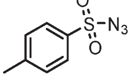
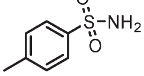


Figure 2. Energy-dispersive X-ray spectra of Cu.

Table 2. Reduction of Aromatic Azides by Cu Nanoparticles/$HCOONH_4$

entry	substrate	time (h)	product	yield (%)[a]	ref[b]
1		8		83	4
2		8		76	11a
3		8		79	11b
4		8		81	11c
5		8		77	11d
6		7		83	11d
7		7		91	12a
8		8		84	4
9		11		72	4
10		10		84	14a
11		10		78	14b
12		12		72	4
13		9		82	12b
14		11		81	12c
15		10		75	13a
16		10		71	13b
17		12		65	4
18		12		63	4
19		9		82	4
20		10		79	-
21		7		73	13c
22		7		81	13c

[a] Yields refer to those of purified products characterized by IR and ^1H and ^{13}C NMR spectroscopic data. [b] The known compounds are identified by comparison of their spectroscopic data with those reported.

Thus, in a typical experimental procedure, a mixture of aryl azide, Cu nanoparticles, and ammonium formate in water was heated under reflux for a certain period of time (TLC). Standard workup and purification by column chromatography provided the pure product.

Copper nanoparticles were prepared from copper sulfate by reaction with hydrazine hydrate in ethylene glycol.[10] The particle sizes are in the range of 6−8 nm as observed in transmission electron microscopy (TEM) (Figure 1). The identity of the particles as being of copper was established by energy-dispersive X-ray spectroscopy (EDS) (Figure 2).

Several substituted aryl azides were reduced by this procedure to produce the corresponding aromatic amines. The results are presented in Table 2. Significantly, 4-, 3-, and 2-nitrophenyl azides (Table 2, entries 4−6) underwent clean reaction, giving the corresponding nitroanilines without any reduction of nitro group. These results indicate that reduction of azide functionality is more facile than that of the nitro group by the copper nanoparticles/$HCOONH_4$ reagent system.[4] The nitro group at the 2-position did not pose any steric constraint (Table 2, entry 6). The nitrile, ketocarbonyl, carboxylic ester, carboxylic acid, amide, *O*-allyl, *N*-allyl, OMe, F, Cl, Br, and I remained unaffected in the reduction of the corresponding azides bearing these functionalities. The *O*-benzyl functional group is also compatible with this procedure (Table 2, entry 17). 6-Azidoquinoline was reduced to 6-aminoquinoline, keeping the heterocyclic ring intact. 1,4-Diazobenzene was reduced to 4-azidoaniline with selective reduction of one azido group. Significantly, use of excess (3 equiv) Cu nanoparticles and ammonium formate also reduced only one azido group. Methyl sulfonyl azide and 4-methylphenyl sulfonyl azide (Table 2, entries 21 and 22) also underwent clean reductions to the corresponding amides by this procedure. Many conventional procedures involving hydride reducing agents, metals, and hydrogenation failed to give such broad spectrum of selectivity.[5c,8]

In general, all of the reactions are clean and high yielding. The azides are easily prepared following a reported procedure.[7] The reductions are not at all effective with Cu nanoparticles alone in the absence of ammonium formate. On the other hand, the reaction was also not initiated using ammonium formate alone in the absence of Cu nanoparticles. A combination of Cu nanoparticles and ammonium formate in water at 100 °C is essential for a successful reaction. The rate of reduction based on the progress of reaction with time (NMR) for a particular substrate is found to be uniform (Figure 3).

To establish the absolute necessity of Cu(0) nanoparticles for this reduction, a comparison of results of a few representative reactions with those by freshly prepared metallic Cu (prepared by reaction of $CuSO_4$ and Zn dust[15]) is presented in Table 3. These results showed only a marginal activity of metallic Cu powder, whereas much higher activity was observed using Cu nanoparticles during the transfer hydrogenation process using ammonium formate[16] under the reaction conditions. To understand the reaction pathway, we carried out the reaction in the presence of TEMPO (2,2,6,6-tetramethylpiperidine *N*-oxide) and we did not find any effect of this radical quencher, indicating a nonradical process. Like Pd hydride formation from Pd nanoparticles,[3a] initially we considered the intermediacy of CuH. However, the formation of CuH under the reaction conditions in water is very unlikely. Moreover, our attempts to trap CuH with ligands such as Ph_3P did not succeed. The reduction of azides requires only a catalytic amount of Cu nanoparticles, although an optimum amount is necessary for a successful reaction. Thus, we ruled out the formation of free CuH. We observed a gradual change of pH (6.91 to 6.41) of the reaction medium toward the acidic range with the progress of the reaction (Table 4). Thus, it is more likely that Cu nanoparticles dissociate the H_2 molecule,[3a] generated from ammonium formate,[16] and adsorb hydrogen onto its surface. We suggest that a Cu(0) nanoparticle, with its surface hydrogen, interacts with the azide, forming a type of weak complex like **A**, which then transfers hydride to azide, leaving a proton on the Cu surface that eventually makes it acidic. To check whether the drop in pH is due to liberation of acidic CO_2 in the reaction process,[17] we performed another experiment using hydrogen gas in place of ammonium formate and observed a similar pH change from 6.91 to 6.45, indicating this change of pH as an inherent characteristic of the process. This transfer process is repeated to provide the intermediate **C** via **B**, leading to the product, as outlined in Scheme 2. This adsorbed surface hydrogen is moderately activated, and thus it facilitates the reduction of azides with high selectivity.[18] It may be assumed that the reactivity observed with Cu nanoparticles may arise from the synergism of small Cu nanoparticles to activate the H_2.[3d]

The water deactivates the Cu nanoparticles after one reaction, and the catalyst cannot be used further; however, when the reaction is carried out in DMF under argon, the Cu nanoparticles can be used for two more cycles although they are gradually deactivated in contact with air and moisture during workup. Nevertheless, we chose water as a reaction medium over DMF as water is green and cost-effective.

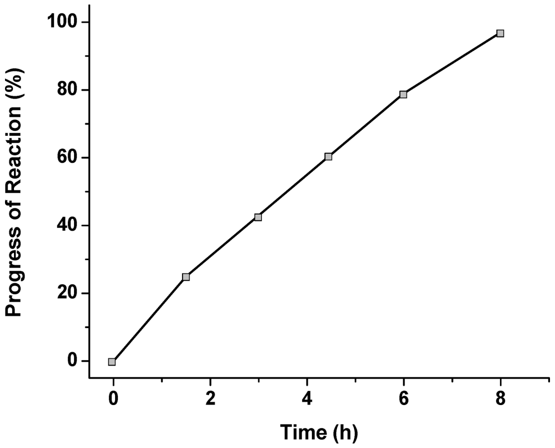
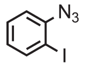
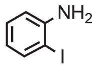
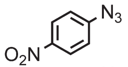
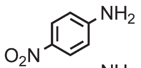
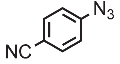
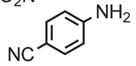
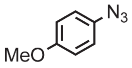
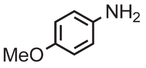


Figure 3. Rate of progress of reduction with time.

Table 3. Comparison of Results of Reductions of Aromatic Azides Using Metallic Cu Powder with Cu Nanoparticles

entry	substrate	time(h)	product	yield(%)[a] Cu NPs	yield(%)[a] metallic Cu powder
1		10		75	7
2		8		81	11
3		7		91	14
4		12		72	12

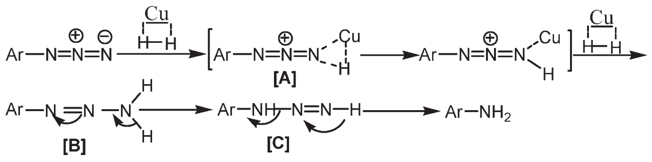
[a] Yields refer to those of purified products characterized by IR and ^1H and ^{13}C NMR spectroscopic data.

Table 4. Measurement of pH during Reduction of 1-Azido-4-nitrobenzene[a]

entry	time (h)	pH
1	0	6.91
2	2	6.83
3	4	6.60
4	6	6.56
5	8	6.41

[a] The reaction was performed at 100 °C, and the pH was measured at room temperature after cooling the reaction mixture.

Scheme 2. Proposed Mechanism



In conclusion, we have developed a new protocol for hydrogenation utilizing hitherto unexplored adsorbed hydrogen on Cu nanoparticle surfaces for the reduction of aryl azides to the corresponding amines. To the best of our knowledge, we are not aware of any report using Cu nanoparticles as a catalyst surface for hydrogenation. The operational simplicity, excellent chemoselectivity, high yields, use of water as reaction medium, cost effectiveness of catalyst, and compatibility with a wide spectrum of functional groups make this procedure more attractive. More significantly, this demonstrates the potential of Cu nanoparticles as a catalyst surface for hydrogenation and promotes further investigation for reduction of useful functionalities.

EXPERIMENTAL SECTION

Representative Experimental Procedure for Reduction of Aromatic Azides to Aromatic Amines (Table 2, entry 4). A mixture of 1-azido-4-nitrobenzene (164 mg, 1 mmol), Cu nanoparticles (32 mg, 0.5 mmol), and ammonium formate (315 mg, 5 mmol) in water (8 mL) was heated at reflux with stirring for 8 h (TLC). After cooling, the reaction mixture was extracted with ethyl acetate (3 × 10 mL). The extract was washed with water and brine and dried over Na_2SO_4. The crude product was purified by column chromatography over silica gel (hexane/ethyl acetate, 8:2) to afford pure 4-nitroaniline (112 mg, 81%) as a yellow solid: mp 147 °C ; IR (KBr) 3433, 3327, 3097, 1627, 1523, 1348, 1265, 736 cm^{-1}, ^1H NMR (300 MHz, DMSO-d_6) δ 6.58 (d, J = 9 Hz, 2H), 6.68 (s, 2H), 7.92 (d, J = 9 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 112.4, 126.4, 135.7, 150.7. These data are in good agreement with the reported values.[11c]

All of these products are known compounds except one (Table 2, entry 20). The known compounds are identified by comparison of their spectroscopic data (IR, ^1H NMR, ^{13}C NMR) with those reported (see references in Table 2). The unknown compound was characterized by its spectroscopic data (IR, ^1H NMR, ^{13}C NMR, and HRMS). These data are provided below.

***N*-Allyl-*N*-(4-aminobenzyl)butan-1-amine (Table 1, entry 20):** Yellow liquid; IR (neat) 3437, 3350, 3215, 3074, 3003, 2955, 2929, 2870, 2862, 2794, 1622, 1516, 1454, 1437, 1417, 1367, 1274, 1172, 1122, 1070, 995, 918, 848, 823 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.86−0.90 (m, 4H), 1.247−1.331 (m, 3H), 2.40 (t, J = 7.5 Hz, 2H), 3.05 (d, J = 6.5 Hz, 2H), 3.46 (s, 2H), 3.53 (s, 2H), 5.11 (d, J = 10 Hz, 1H), 5.16 (d, J = 18.5 Hz, 1H), 5.84−5.92 (m, 1H), 6.63 (d, J = 8 Hz, 2H), 7.09 (d, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 20.6, 29.1, 52.9, 56.5, 57.5, 114.9, 117.0, 129.3, 130.1, 136.2, 145.2; HRMS m/z calcd for $C_{14}H_{23}N_2$ $[M + H]^+$ = 219.1861, found 219.1856.

ASSOCIATED CONTENT

Supporting Information. Copies of ^1H and ^{13}C NMR spectra of all products listed in Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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