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Highly chemoselective reduction of azides to amines by Fe(0) nanoparticles in water at room temperature

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ABSTRACT

A highly chemoselective reduction of aryl, heteroaryl, acyl and sulfonyl azides to the corresponding amines has been achieved by Fe(0) nanoparticles in water at room temperature in the absence of external hydride source. Several readily reducible functionalities including alkene, alkyne, S-S linkage, OTBDMS remain unaffected during reduction.

Introduction

The organic azides are of much importance as they have versatile applications in the synthesis of a wide variety of useful compounds such as triazoles, tetrazoles and other heterocycles.[1] The reduction of azides provides an easy access to amines which play important role in both biology and chemistry as the amines constitute the vital unit for many useful pharmaceuticals, biologically active compounds, natural products, rubber and dyes.[2] As azides are easily accessible from halides and sulfonates[3] several methods are reported for the preparation of amines from azides.[4] However reduction of azide in the presence of other reducible groups, particularly S-S linkage[5] is difficult to achieve. Notably, many biologically relevant molecules such as DNA oligonucleotides contain S-S linkage along with amine functionality (Fig. 1) and thus reduction of azide in the presence of S-S linkage is of much importance. Several procedures involving hydride reducing agents,[6a] triphenyl phosphine,[6b] radical initiators,[6c] Zn(BH$_4$)$_2$,[6d] Cl$_2$InH,[6e] molybdenum xanthate/PhSiH$_3$,[6f] metal catalyzed hydrogenations[6g] etc. were employed. However, these protocols are associated with one or more of the limitations such as chemoselectivity, general applicability, cost efficiency, harsh reaction conditions and tedious work up procedures.[7]

In general, hydrogenations over transition metal nanoparticles provide an efficient tool for reduction due to the availability of more active surface area of the metal nanoparticles compared to the parent metals.[8] Catalytic hydrogenations in the presence of transition metal nanoparticle based on Pd,[9] (Pt, Ru)[10] and Cu[11] have been accomplished in the presence of a co-reductant like hydrazine hydrate, ammonium formate, methanol etc. However the high cost and toxicity of these metals led to find alternate economical, and environmentally benign candidates. The consideration of Fe-catalysis receives prime importance as iron is one of the most inexpensive, abundant and environmentally friendly transition metals. Recently a couple of methods based on Fe such as Fe(acac)$_3$/N$_2$H$_4$·H$_2$O/MW(150 °C)[4h] and Fe$_3$O$_4$

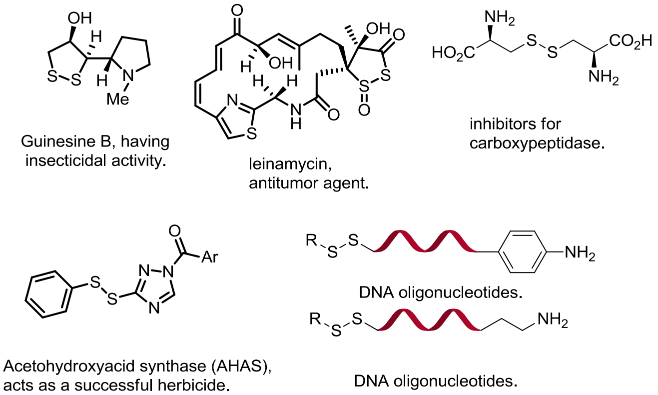

Fig. 1. A few biologically active molecules containing S-S bond.

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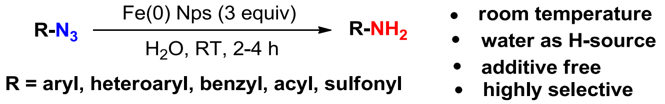
NPs/$N_2H_4{\cdot}H_2O$/120 °C[12] have been reported for the reduction of azides to amines. However, these Fe-catalyzed procedures are associated with use of high temperature and excess co-reductant for efficient reduction and also poor chemoselectivity with aryl nitro-azides.[12] Thus a simpler and greener protocol with high chemoselectivity is highly desired. In continuation of our interest on application of metal nanoparticles[4n,11,13] we report here a highly chemoselective reduction of aryl/heteroaryl azides to amines using Fe(0) nanoparticles[14] in water at room temperature in the absence of any external co-reductant as H-source (Scheme 1).

Our primary consideration in selective reduction of the azide moiety is to find a target specific reducing agent which is just enough to reduce the azide functionality in the presence of other reducible functionalities on the aromatic ring. As Fe(0) nanoparticles are more reactive compared to Fe(0) powder, better co-ordination of Fe NPs with water molecules is expected and in this situation the electrophile hydrogens of water are likely to attain pseudo-hydride character and such mild hydride is considered enough to reduce the aromatic azide moieties keeping the other reducible functionalities in the aromatic ring unaffected.



Scheme 1. Highly selective water mediated azide reduction by Fe(0) NPs.

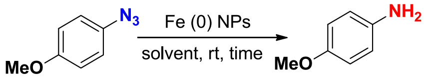
Table 1
Standardization of reaction conditions.

Entry	Fe(0)Nps (equiv.)	Solvent	Time (h)	Yield (%)[a]
1	3	Toluene	12	–
2	3	Dichloromethane	12	–
3	3	DMF	12	Trace
4	3	DMSO	12	Trace
5	3	CH_3CN	12	–
6	3	H_2O	2	95
7	3	MeOH	12	–
8	2	H_2O	4	35

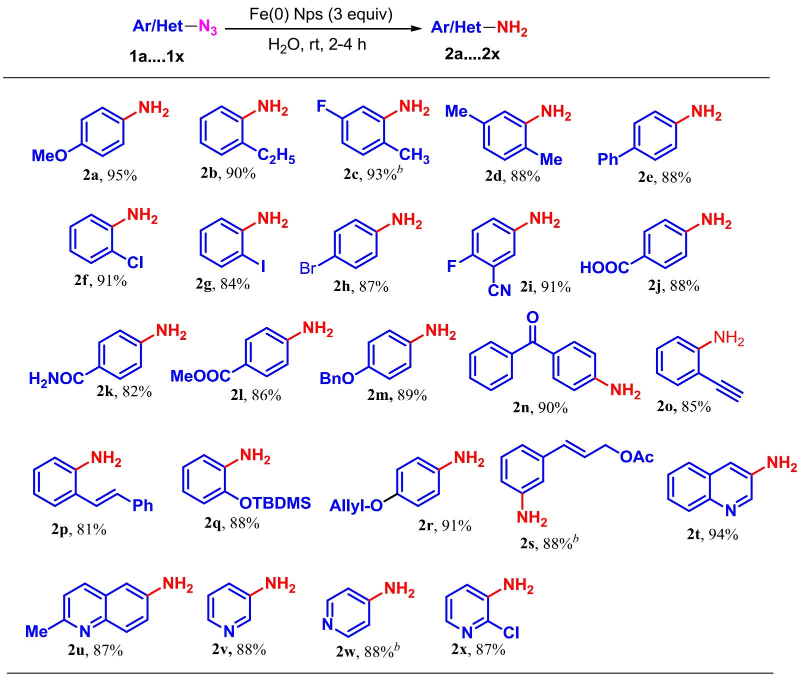
[a] *Reaction conditions*: azidobenzene (1 mmol), rt, solvent (5 ml).

Results and discussion

The Fe nanoparticles were obtained by a reported procedure using $FeCl_3$ and sodium borohydride and used as such.[14] Aryl azide (1 mmol) was stirred with Fe(0) nanoparticles (3 mmol) in water at room temperature for a required period of time (TLC). Extraction by ethyl acetate and standard work up provided the product. The Fe(0) NPs obtained by a different procedure using tea extract[15] without using any hydride reducing agent also provides the same result.



To standardize the reaction conditions several experiments have been performed by varying the reaction parameters such as solvent, time, amount of Fe(0) Nps etc for a representative reduction of azidobenzene (Table 1). Solvents such as toluene, dichloromethane (DCM), N,N-dimethyl formamide (DMF), dimethyl sulfoxide (DMSO), acetonitrile failed to produce satisfactory results (Table 1, entries 1–5). The reaction went efficiently in water using 3 equivalents of Fe nanoparticles (Table 1, entry 6). However, the reaction furnished only 30% yield using 2 equivalents of Fe(0) NPs in water (Table 1, entry 8). Interestingly, a protic solvent methanol failed to initiate the reduction process. Thus water has a decisive role in this reaction. A wide range of substituted aromatic azides have been reduced successfully by this procedure to produce the corresponding aromatic amines. The result was summarized in Scheme 2. The easily reducible functionalities such as -COPh (**2n**), -COOMe (**2l**), –COOH (**2j**), -CN (**2i**), -$CONH_2$ (**2k**), -OAc (**2s**) and the halogen moieties –F (**2i**), -Br (**2h**), -I (**2g**), and -Cl (**2f**) in the aromatic ring remained unaffected during the reaction. The reactions went successfully with electron donating



Scheme 2. Fe(0) nanoparticles mediated reduction of aromatic and heteroaromatic azides.