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A NOVEL APPROACH TOWARDS CHEMOSELECTIVE REDUCTION OF NITRO TO AMINE

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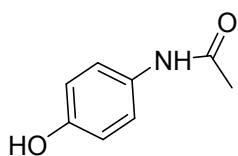
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Abstract: Chemo selective reduction of a wide range of aromatic nitro compound has been performed by using inexpensive Zn powder and CuSO₄ system in water medium at room temperature. This system has high tolerance to other highly reducible groups present in nitro substance along with high conversion and selectivity. This chemo-selective reduction also provides a facile route for the synthesis of other industrially important fine chemicals or biologically important compounds where other highly reducible groups are present in close proximity to the targeted nitro groups.

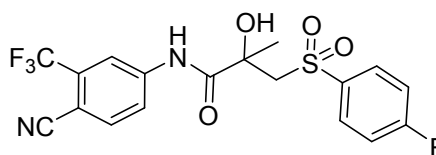
Key words: Chemo selective, non-hazardous reducing agents, aromatic nitro compound, metal salt.

Introduction:

Substituted aromatic amines are very important feedstock for synthesis of many significant fine chemicals like agrochemicals, dyes, biological active compounds, polymers and various other industrially important compounds.^[1] Aromatic amines also form substructures of many pharmaceutical compounds. An acetyl derivative of *p*-aminophenol known as Paracetamol^[2] 1a, a widely used analgesic and antipyretic. Bicalutamide^[3] 1b has a *p*-cyano-*m*-trifluoroaniline component in its structure, is a non-steroidal antiandrogen administered orally for the treatment of prostate cancer and hirsutism.



Paracetamol 1a
(Analgesic, Antipyretic)



Bicalutamide 1b
Anticancer (Prostate)

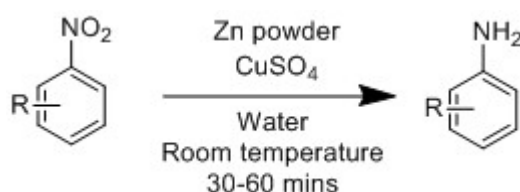
Vastly employed method for the preparation of substituted aromatic amines is reduction of corresponding nitro substrates. But selective reduction of a functional group in presence of other

functional group which is also reducible is often a very difficult task.^[4] In general employing transition metal catalyst results in reduction of olefinic and halogeno functions than that of N-O bond. Moreover, traditional non-catalytic processes often produce large amount of waste and hence environmentally non-sustainable.^[5] Catalytic hydrogenation is often a convenient and clean method but lacks selectivity.^[6] Another alternative to catalytic hydrogenation, catalytic transfer of hydrogen is also introduced for reduction purpose in which hydrocarbons, alcohols, organic acids and their salts, hydrazine etc. were used as source of hydrogen with variety of metal based catalysts.^[7-11] However, it's worth a note the main disadvantages to these procedures include the catalysts being incompatible to the acid-sensitive functional groups and requires higher reaction temperature, longer reaction time and suffers from low or mixed yield of products.^[12] Recent successful attempt of reducing nitroarenes selectively by employing CO₂ gas at very high pressure resulting in-situ generation of carbonic acid, which further gets associated with reducing metals and performs the selective reduction process.^[13] Nonetheless, the requirement of high CO₂ pressure in order to activate the reducing metal and generate carbonic acid, and high reaction temperature are the main drawbacks of the scheme. Another recent report worth mentioning is reduction of nitro compounds to corresponding amines selectively in presence of photo catalyst and Pd/CeO₂, CdS.^[14] Despite the scheme shows high selectivity and considerable activity in presence of noble metals, costly noble metals are the major hurdles in this article. Recent communications on catalytic systems based on Co-Co₂B, Fe₂O₃, Co₂O₃ etc. show high activity and directs toward the development of more economical efforts.^[15-17] But most of the contrivance uses harsh condition which is undesirable. Pure water has been employed as solvent by Poliakoff and Boix^[18] using metallic reducing agents for selective reduction of nitroarenes at 250°C. With iron powder the yield reported is only 10% of substituted aniline under mentioned reaction condition. Modification has been done by Wang et al.^[19] and iron powder has been replaced by nano-sized activated iron for direct and selective reduction of nitroarenes in water^[20]. Though good yield has been achieved, the temperature requirement was still 210°C. In addition to that preparation of nano-sized particle and maintaining the size requires extra effort and expense.

There exist very few reports on eco-friendly, inexpensive metal catalysts or reducing agents that can promote reduction of nitro groups selectively at room temperature. And needless to mention water based conversions are of critical importance in organic chemistry. Therefore, development of a cost effective, greener, easily achievable, less time consuming reaction scheme with non-hazardous reducing agents is highly desirable. Regarding this context our interest was

solely on developing a new scheme using low cost, greener, metal-metal salt based reducing agent and to carry out the reaction on most easily available solvents like water and ethanol.

Herein, we report selective reduction of nitroarenes at room temperature in presence of non-hazardous, inexpensive and easily available metal salt like CuSO_4 and Zn metal in water solvent system within 30 minutes – 60 minutes. (Scheme 1)



Scheme 1.Reduction of aryl nitro to corresponding amine

RESULTS AND DISCUSSIONS:

Aromatic nitro and substituted nitro compounds were reduced in good yield to the corresponding amino compounds under mild conditions in the presence of low cost and easily available metal and metal salt Zn and CuSO_4 respectively in water, with single product. The compound obtained were monitored by TLC and separated by column chromatography. The general scheme and reaction are shown in **scheme I**.

Table1:^aOptimizationof the reaction condition for reduction of Nitroarenes to the corresponding Anilines.

Entry	Metal/Metal salt	Solvent	Time (min)	Temperature (°C)	^b Yield (%)
1	Fe/ CuSO_4	Nil	180	R.T	Nil
2	Zn	H_2O	180	R.T	Nil
3	Fe	H_2O	180	R.T	Nil
4	CuSO_4	H_2O	180	R.T	Nil
5	Fe/ CuSO_4	H_2O	180	R.T	68
6	Fe/ CuSO_4	$\text{H}_2\text{O}+\text{EtOH}$	180	R.T	60
7	Fe/ CuSO_4	EtOH	180	R.T	56
8	Cu/ CuSO_4	H_2O	180	R.T	65
9	Zn/ CuSO_4	H_2O	180	R.T	95
10	Zn/ FeSO_4	H_2O	180	R.T	80

11	Zn/ZnSO ₄	H ₂ O	180	R.T	76
12	Zn/NiSO ₄	H ₂ O	180	R.T	72
13	Zn/CuSO ₄	H ₂ O	120	R.T	95
14	Zn/CuSO ₄	H ₂ O	60	R.T	94
15	Zn/CuSO ₄	H ₂ O	30	R.T	70
16	Zn/CuCl ₂	H ₂ O	60	R.T	84
17	Zn/Cu(OAc) ₂	H ₂ O	60	R.T	72
18	Zn/CuBr ₂	H ₂ O	60	R.T	66
19	Zn/CuSO ₄	H ₂ O	60	60	89
20	Zn/CuSO ₄	H ₂ O	60	80	87

^aReaction of o-

nitrobenzaldehyde (1 mmol), Zn (3 mmol), CuSO₄ (3 mmol) in water on magnetic stirrer

^bIsolated yield

Table 2: ^aOptimization of amount of Zn and CuSO₄

Entry	Zn (mmol)	CuSO ₄ (mmol)	Time (min)	^b Yield (%)
1	1	1	60	54
2	2	2	60	67
3	3	3	60	94
4	4	4	60	95

^aReaction of o-nitrobenzaldehyde (1 mmol) in water on magnetic stirrer

^bIsolated yield

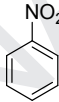
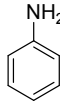
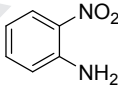
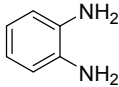
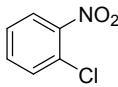
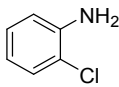
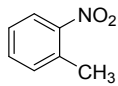
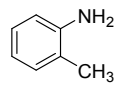
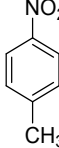
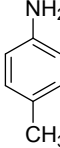
At first, we investigated the influences of solvents, additives, metals, time and temperature on the reduction of aromatic nitro to its corresponding amine (Scheme 1, Table 1). The reduction of selected model nitro substrate, o-nitrobenzaldehyde revealed that high conversion and selectivity could be achieved within 60 min in the presence of water. Entry 1 demonstrates that the reaction could not proceed in absence of solvent. From entry 1-7 (Table 1) we conclude that water is the superior solvent for the process, as in this process hydrogen ion is efficiently supplied by water. Further water is the most easily available and green solvent which enhances the cost effectiveness of our scheme.

We found that both metal and additive were necessary for this reduction process (Table 1, entries 3, 4, 5). Compared with that CuSO₄, other additives were inferior in terms of yield of product and reaction time. Entry 5, 8, 9 (Table 1) implies that here Zn metal play a vital role for nitro reduction. Electro chemical series also support our result. The reduction potential of applied metal and additive is as follows, $E^0_{Zn^{2+}/Zn} = -0.76$, $E^0_{Fe^{2+}/Fe} = -0.44$ and $E^0_{Cu^{2+}/Cu} = +0.34$, which clearly indicates the reduction potential difference between Zn and Cu is higher, which facilitate

the transfer of electrons in the process than the other couples. This concept is in accordance with our observed results (Table 1). But entry 11 also suggest that acidic nature of metal salts is indebted for reduction and reduction potential difference between metals amplify the potency of the process. Entries 9 to 14 implies that if we lower the time from 180 minutes to 60 minutes the yield of the product more or less same, but when we were tried to decrease the time from 60 minutes to 30 minutes then product's yield decreases remarkably. Now we were tried to optimize temperature. With the help of entries 14, 19, 20 we observed that if we increase the temperature yield of the product decreases. So with respect to time, temperature, metal/metal salt entry 14 is the optimized condition. Further we optimized the amount of Zn and CuSO₄ required (Table 2). We started our optimization with 1 mmol each. The yield was considerable but low. As the amount of reagents has been increased and we reached our maximum yield at 3 mmol Zn and 3 mmol CuSO₄. No further increase in yield has been observed with increasing reagents. Considering the above mentioned points, under atmospheric pressure, 60 minutes of reaction time and room temperature is finalized as the optimum condition for this reaction (Table 1).

This procedure is followed for all of the reactions listed in Table(3)

Table 3: ^aZn and CuSO₄ mediated reduction to amines

Entry	Reactant	Product	Time (min)	^b Yield (%)
1			50	90
2			30	85
3			30	85
4			30	95
5			30	92

6			40	80
7			30	93
8			30	93
9			30	94
10			40	93
11			50	87
12			60	89
13			50	92

^aReaction of nitro compound (1mmol), Zn (3 mmol), CuSO₄ (3 mmol) in water at room temperature for different time intervals on magnetic stirrer.

^bIsolated yields

On the basis of the table 1, reduction of other nitroarenes were carried out by using Zn/CuSO₄ in water without any organic solvent at room temperature under atmospheric pressure (Table 2). Aldehyde, halogens, nitrile, acid functionality present in aromatic ring remained unaffected during reduction of the corresponding nitro benzene by this process (entries). These results demonstrate that we can employ this technique to nitroarenes containing reduction-sensitive substituent. The reaction took place smoothly and chemoselectively to produce corresponding anilines in moderate to high yields (entries).

Plausible mechanism:

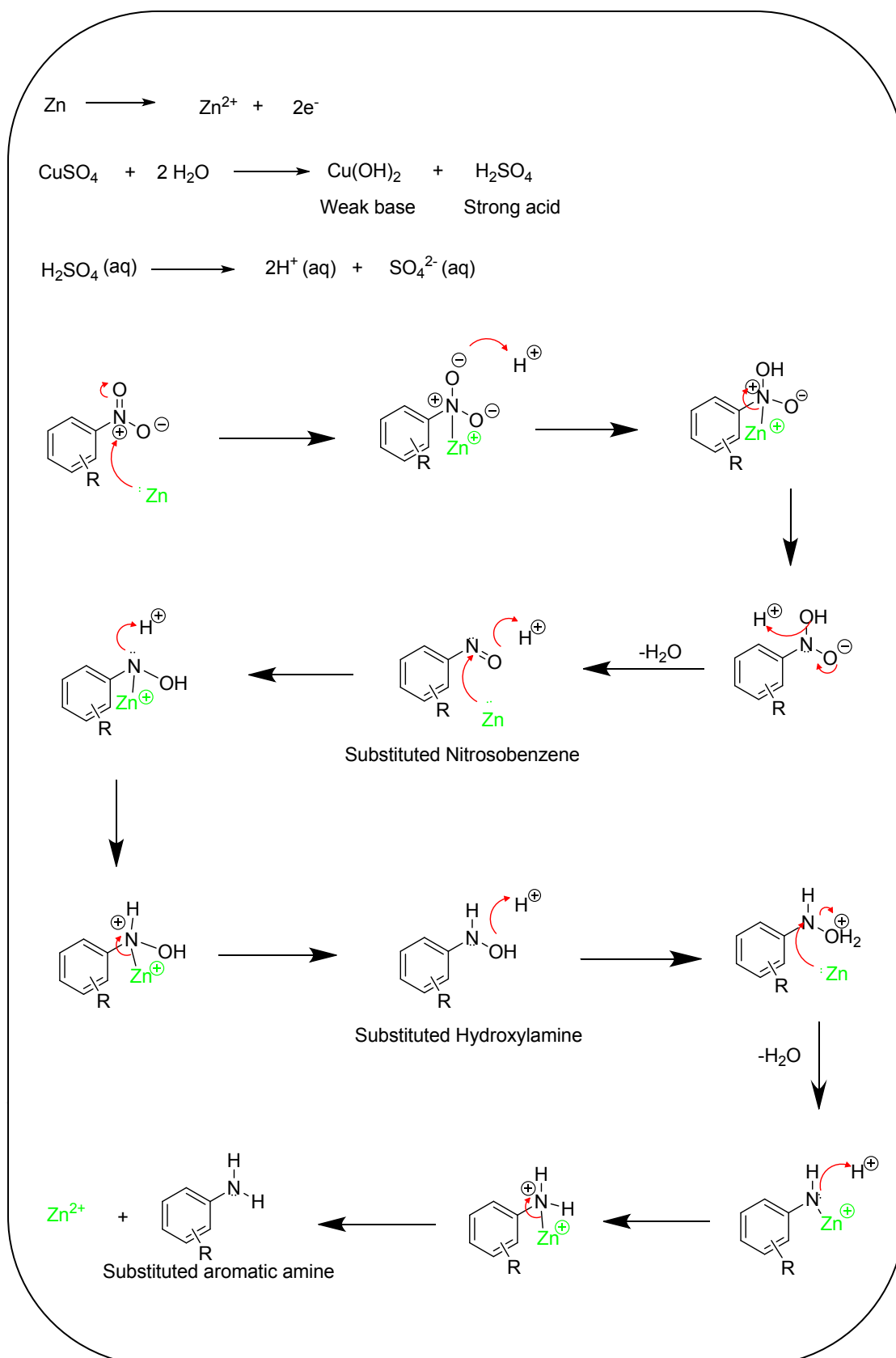


Fig 2. Plausible mechanism for synthesis of amine from nitro derivative

A plausible mechanism has been shown in fig 2. For the nitro reduction we need source of electron and hydrogen ion. From the mechanism we can see that in our reaction electrons are supplied by Zn metal and hydrogen ions are supplied by H₂O and here CuSO₄ increase the acidity of the medium which facilitate the reaction leading to the corresponding amine

For reduction of nitroarenes leading to aromatic amines with Zn metal, methods employing Zn/HCl^[21], Zn/aq. NaOH/EtOH^[22], Zn/NH₃^[23], Zn/CaCl₂/EtOH^[24], Zn/near-critical water^[25], Zn/Ru-complex/H₂O/KOH^[26], Zn/ether/H₂O^[27], Zn/CO₂/H₂O^[28], Zn/SiO₂-PEG^[29] have been reported. However, since the conventional methods required organic solvents and/or drastic conditions using an irritant reagents such as NH₃, corrosive reagents HCl, NaOH, it is difficult to contend that these methods are environmentally harmonious. On the other hand, the reaction time is prolonged for Zn/NH₃ (24h), Zn/Ru-complex/H₂O/KOH (16h), Zn/ether/H₂O (5-11h). In addition, some special apparatus and high temperature is required for some processes. To overcome these hurdles, we have introduced our scheme using Zn metal, CuSO₄ and water at room temperature. The greatest advantage of our method compared with other methods is easy handling, cost effective, environmentally benign.

All of this products are known compounds and were easily characterized by comparison of their spectra with those reported.

Experimental section:

Representative Experimental Procedure for Reduction of Aromatic Nitro Compounds.

A mixture of nitro compound (1 mmol), Zn powder (3 mmol), CuSO₄ (3 mmol) in 5 mL water at room temperature was stirred on a magnetic stirrer. The progress of the reaction was monitored by TLC. After completion of the reaction, the metallic part was filtered off. The filtrate was poured into 100 mL water and extracted with ethyl acetate, washed several times with water. Evaporation of solvent followed by column chromatography over basic alumina using petroleum ether/ethyl acetate (3:1) as eluent to afford the pure aryl amines (). The spectroscopic data (IR, ¹H NMR,) of this compound are in good agreement with those reported.

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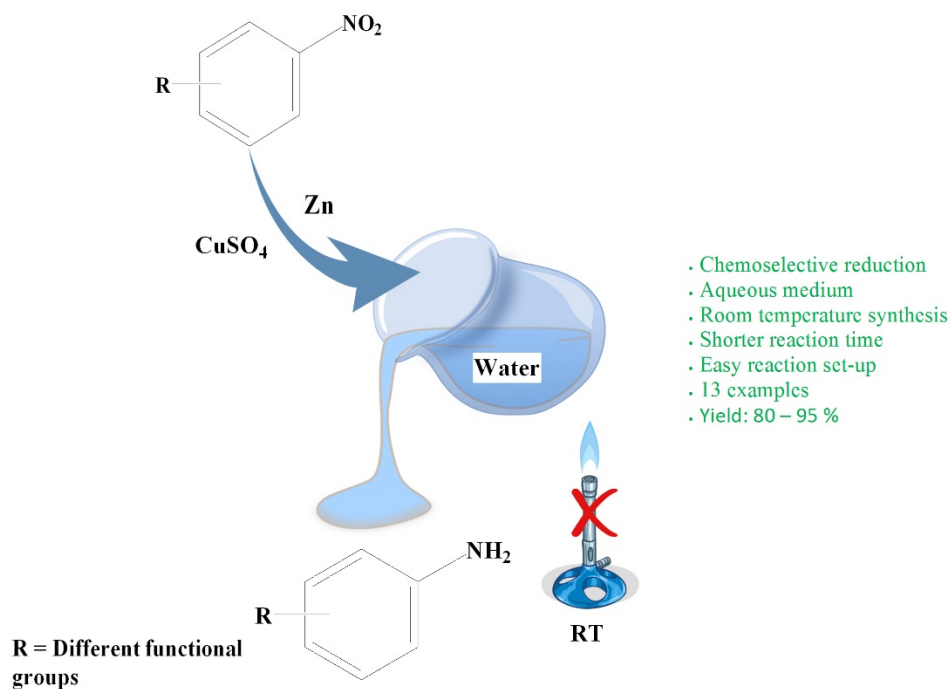
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A Novel Approach Towards Chemoselective Reduction of Nitro to Amine

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HIGHLIGHTS

1. Chemo selective reduction
2. high tolerance to other highly reducible groups
3. clean method
4. selective reduction of nitro arenes at room temperature