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Synthesis of azo compounds by nanosized iron-promoted reductive coupling of aromatic nitro compounds

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Dedicated to Professor Miguel Yus on the occasion of his 60th birthday

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Abstract

Treatment of a variety of aromatic nitro compounds with the active-iron based reducing system composed of $FeCl_2{\cdot}4H_2O$, an excess of lithium powder and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB, 5 mol %) in THF at room temperature, led to the formation of the corresponding symmetrically substituted azo compounds in good yield, resulting from a reductive coupling process. Some other functionalities including carbonyl, halogen, amino and hydroxyl groups, demonstrated to be compatible with the reaction conditions, giving none reduced or coupled by-products. In all cases, the azo compounds formed have not experienced over-reduction to the corresponding hydrazo or amino derivatives even upon prolonged heating or using an excess of the reducing system.
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Keywords: Active-iron; Reductive coupling; Nitro compounds; Azo compounds

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Aromatic nitro compounds are an important class of organic industrial products, and precursors of other valuable organic compounds. The reduction of nitroaromatics,[1] for instance, can lead to different versatile products, a basic medium usually favours their conversion to azoxy, azo, and hydrazo derivatives, whereas strongly acidic conditions or catalytic hydrogenation lead to the corresponding amines.[1–7]

Although the reduction of aromatic nitro compounds has been brought about by a large number of methods,[8] many of them show important limitations including harsh reaction conditions, expensive reagents, incompatibility with other functional groups present in the molecule, and the lack of selective access to only one of the possible reduction products.[9]

On the other hand, azo compounds which have been widely utilised over the years as dyes and analytical reagents,[10] have more recently found advanced potential applications in various fields such as biomedicine,[11] organic synthesis[12] and as materials with excellent optic and photoelectric properties.[13] Direct synthesis of azo derivatives in good yields can be accomplished by the reduction of nitroaromatics with metal hydrides,[14] zinc in strongly alkaline medium,[15] or dicobalt octacarbonyl.[16] Many other methods for the preparation of azo compounds have been described in the literature,[8a,12,17,18] most of them giving low yields and undesired side reactions. In addition, they require harsh conditions or can generate dangerous pollutants for the environment.[17] Consequently, new methodologies, milder reaction conditions and inexpensive reagents for the selective synthesis of azo compounds are welcome.

In recent years, we have worked with new active-metal-based reducing systems, consisting of a mixture of hydrated salts of nickel, copper, or iron, and lithium in the presence

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of a catalytic amount of an arene as electron carrier. The most studied $NiCl_2{\cdot}2H_2O$–Li–arene(cat.) system was very effective in the reduction of a wide variety of organic functional groups,[19] including aromatic azo, hydrazo and azoxy compounds.[20] The analogous copper-based system, $CuCl_2{\cdot}2H_2O$–Li–arene(cat.), was successfully applied to the reduction of carbonyl compounds and imines,[21] as well as that of sulfonates.[22] With regard to the more economical $FeCl_2{\cdot}4H_2O$–Li–arene(cat.) system, it showed a remarkable behaviour in the stereoselective reduction of cyclic ketones,[23] and in the hydrodehalogenation of a wide variety of organic halides, including aryl fluorides and polychlorinated aromatics.[24] Recently, we found that the active-iron generated by this methodology consisted of very reactive, monodispersed spherical iron(0) nanoparticles, most of them (83%) between 1.5 and 3.5 nm as shown by transmission electron microscopy (TEM). A typical TEM micrograph and size distribution graphic are depicted in Figures 1 and 2, respectively.

As part of a wider work in the reduction of different organic functionalities, and prompted by the known ability of iron in promoting the reduction of aromatic nitro groups, we decided to evaluate our active-iron-based reducing system in performing that transformation.

We wish to report herein our results on a reduction methodology of nitroaromatics that leads to a facile and selective preparation of aromatic azo compounds, under mild reaction conditions, based on the use of iron(0) nanoparticles, generated in a simple an economic way from commercially available iron(II) chloride tetrahydrate, lithium and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB) as electron carrier.

The reaction of a series of aromatic nitro compounds with a mixture of iron(II) chloride tetrahydrate (1.0 mmol), an excess of lithium powder (1:8 molar ratio, referred to the iron salt), and a catalytic amount of DTBB (0.1 mmol/mmol of iron salt, 5 mol %) in refluxing tetrahydrofuran, led to the formation of the corresponding symmetrically substituted azo compounds in good yields, resulting from a reductive coupling process. Various azo compounds containing additional functional groups such as carbonyl, halogen, amino and hydroxy groups, have been easily synthesised in one step using this methodology.

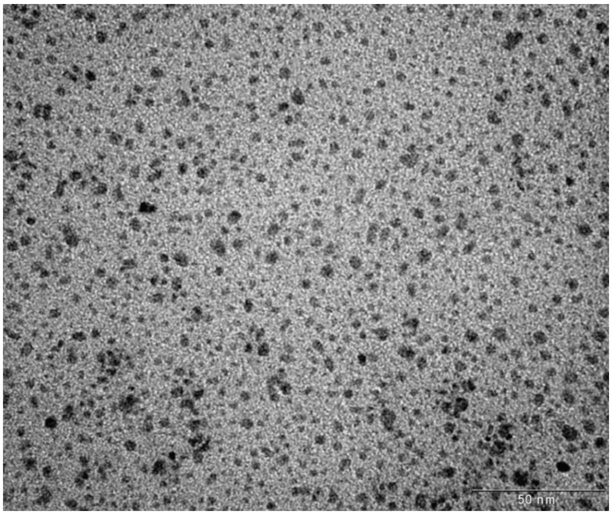


Fig. 1. TEM micrograph of iron nanoparticles.

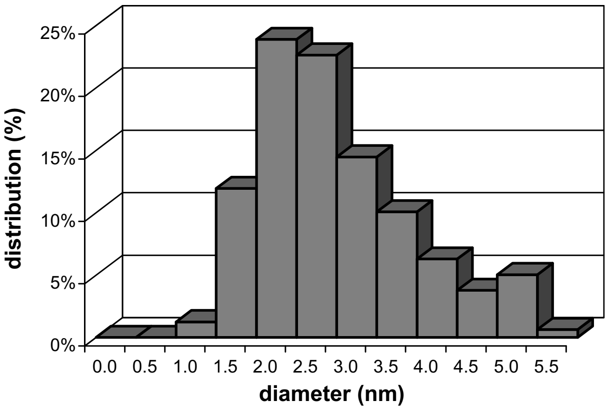


Fig. 2. Size distribution of iron nanoparticles determined by TEM. The sizes were determined for 150 nanoparticles selected at random.

Blank experiments, using nitrobenzene as test compound, demonstrated the necessity of using the hydrated iron salt. Unreacted starting material, and very low conversion (ca. 20%) to a mixture of azobenzene, aniline and nitrosobenzene were obtained without using the mentioned salt. The use of the more expensive anhydrous iron(II) chloride showed similar results to those obtained with the hydrated iron salt, azobenzene being the major reaction product in a slightly lower yield.

Table 1 shows the conditions and results for a series of aromatic nitro compounds. It can be seen that the reduction of nitrobenzene gave azobenzene in excellent yield (Table 1, entry 1). The reducing system was also efficient in the reduction of aromatic nitro compounds bearing additional substituents, that is the case of *p*-, *m*- and *o*-nitrotoluene (Table 1, entries 3–5, respectively), *p*-, *m*- and *o*-nitroaniline, (Table 1, entries 6–8, respectively), and *p*- and *o*-nitrophenol (Table 1, entries 9 and 10), all of which were reduced to the corresponding symmetrical substituted azobenzenes in good yields. The reducing system demonstrated to be highly selective towards the reduction of the nitro group with aromatic nitro compounds bearing other reducible functional groups. Thus, the reaction of halo-substituted nitro compounds (Table 1, entries 12 and 13), yielded the corresponding halogenated azo compound together with minimum amounts of azobenzene (ca. 7%). These results indicate that the nitro group reduction is significantly faster than hydrodehalogenation process, what is in concordance with previously published studies by other authors for the reduction of nitro derivatives mediated by Fe(0) in aqueous media.[25] In the case of *p*-nitroacetophenone (Table 1, entry 14), the reduction to some extent of the carbonyl group in the starting material was observed, yielding ca. 10% of 1-(4-nitrophenyl) ethanol as by-product.

Table 1
Synthesis of azo compounds by iron-promoted reduction of aromatic nitro compounds[a]

Entry	Starting nitro compound	Time (h)	Products[b]	Yield[c] (%)
1	Nitrobenzene	2.5	Azobenzene	97
2	Nitrobenzene	0.5	Azobenzene	11[d]
			Aniline	35[d]
			Nitrosobenzene	23[d]
3	*p*-Nitrotoluene	4.0	4,4′-Dimethylazobenzene	85
4	*m*-Nitrotoluene	4.0	3,3′-Dimethylazobenzene	73
5	*o*-Nitrotoluene	4.5	2,2′-Dimethylazobenzene	79
6	*p*-Nitroaniline	3.0	4,4′-Diaminoazobenzene	83
7	*m*-Nitroaniline	5.0	3,3′-Diaminoazobenzene	69
8	*o*-Nitroaniline	3.0	2,2′-Diaminoazobenzene	78
9	*p*-Nitrophenol	3.5	4,4′-Dihydroxyazobenzene	81
10	*o*-Nitrophenol	3.5	2,2′-Dihydroxyazobenzene	75
11	1-Nitronaphtalene	7.0	1,1′-Azonaphthalene	51[e]
12	*p*-Bromonitrobenzene	2.5	4,4′-Dibromoazobenzene	77[f]
13	*p*-Chloronitrobenzene	2.5	4,4′-Dichloroazobenzene	80[g]
14	*p*-Nitroacetophenone	3.0	4,4′-Diacetylazobenzene	71[h]

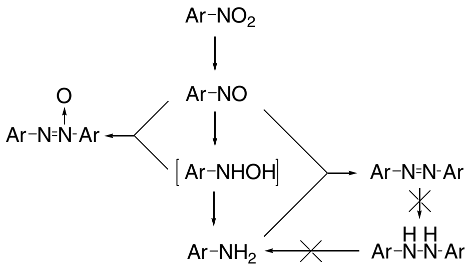
[a] Nitro compound (1.0 mmol), $FeCl_2\cdot 4H_2O$ (1.0 mmol), Li (8.0 mmol), DTBB (0.1 mmol). All reactions were performed under THF reflux.
[b] All isolated products were >95% pure (GLC).
[c] Isolated yield after preparative TLC (silica gel, hexane/ethyl acetate) based on the starting nitro compound.
[d] GLC yield based on the starting nitro compound.
[e] 40% of starting 1-nitronaphtalene recovered.
[f] 14% GLC yield of azobenzene as by-product.
[g] 8% GLC yield of azobenzene as by-product.
[h] 18% GLC yield of 1-(4-nitrophenyl)ethanol as by-product.

With regard to the reactivity of the different substrates tested, it is worth noting that the electronic properties of substituents attached to the aromatic ring did not have any effect on the reduction of nitro groups. Moreover, substrates bearing strong-electron releasing groups (Table 1, entries 6–10), which have been reported as less reactive or inert when reacted with other reducing agents,[26] gave the corresponding azo derivatives in similar yields and in reaction times comparable to that of the aromatic nitro compounds substituted with electron-withdrawing groups (Table 1, entries 12–14). Concerning the steric hindrance effect at the nitro group by substituents at the ortho position, we have only observed an adverse effect for the reductive coupling process in the case of 1-nitronaphtalene (Table 1, entry 11), other ortho substituents such as methyl, amino, or hydroxyl (Table 1, entries 5, 8 and 10, respectively), did not adversely affect the course of the reaction.

Finally, in order to get some information about the plausible reaction pathway, we examined the reduction of nitrobenzene by stopping the reaction at an intermediate stage, leading to the partial conversion of the starting material to a mixture of nitrosobenzene, aniline and azobenzene (Table 1, entry 2). Mechanistically, the complete reduction of a nitro to an amino group is known to follow the reaction pathway depicted in Scheme 1.[8c,27] It is worth noting that we have not detected the formation of arylhydroxylamines as intermediates with all of the substrates tested, probably due to their fast conversion to the corresponding aniline derivatives in the reaction medium. On the other hand, in all cases we observed the presence of azoxyarenes as minor byproducts (3–7%). Then, we decided to test the possible intermediacy of azobenzene and hydrazobenzene in the formation of aniline, and that of azoxybenzene in the formation of azobenzene. We used commercial pure samples of azobenzene, 1,2-diphenylhydrazine and azoxybenzene under the same reaction conditions. We observed that the reduction of N=N, N–N, and N–O (for azoxy derivatives) bonds are ruled out under our iron-mediated reaction conditions.[28] Therefore, the azo products are probably formed by condensation of the nitrosobenzene and aniline intermediates (Scheme 1).[27a] Taking into account that the previously studied nickel-based reducing system readily reduced azo, hydrazo and azoxy derivatives to the corresponding amines,[20] but resulted ineffective against nitroaromatics, it can be concluded that the nature of the transition metal used in the reduction of these nitrogen-containing functionalities is crucial to direct the reaction pathway towards the desired reduction products.

In summary, we have described herein a new methodology which represents a mild, efficient and economical procedure of proven utility in the synthesis of aromatic azo compounds, based on the use of iron(0) nanoparticles generated in a simple an economic way from commercially available iron(II) chloride tetrahydrate, lithium and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB) as electron carrier.

We are now studying other possible synthetic applications and mechanistic aspects of these preliminary findings, and focusing our efforts on the development of a modified methodology for the preparation of unsymmetrical azo compounds.



Scheme 1.

General procedure: A solution of the corresponding nitro compound (1.0 mmol) in THF (5 mL) was added to a mixture of iron (II) chloride tetrahydrate (198 mg, 1.0 mmol), lithium powder (56 mg, 8.0 mmol) and DTBB (27 mg, 0.1 mmol), under nitrogen atmosphere. The reaction mixture, which was initially dark green, changed to black, indicating that iron(0) was formed. Then, the reaction vessel was introduced into a preheated silicon oil bath, at a temperature high enough to ensure the reflux of the solvent. The reaction time was monitored by TLC and GLC. The resulting suspension was diluted with ether (10 mL) and carefully hydrolysed with water (15 mL). The organic layer was dried over anhydrous magnesium sulfate and evaporated (15 Torr) to give a residue, which after purification by preparative TLC (silica gel, hexane/EtOAc) yielded the target pure azo compound. All the products are known compounds and were characterised by comparison of their physical and spectroscopic data with those of commercially availables samples or literature data. The TEM image was recorded at the TEM service of the University of Alicante (Spain) using a JEOLJEM2010 microscope, equipped with a lanthanum hexaboride filament, operated at an acceleration voltage of 200 kV.

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28. Over-reduction of azobenzene to give hydrazobenzene was not observed as a side reaction in the reduction of nitrobenzene, neither prolonging the reaction time (16 h) nor using a large excess of the reducing system (5.0 equiv of $FeCl_2{\cdot}4H_2O$ referred to the starting nitro compound).