Cu-Nanoparticles: efficient catalysts for the oxidative cyclization of Schiffs' bases

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Abstract—Cu-Nanoparticles provide an efficient catalysis for the synthesis of 2-arylbenzoxazoles by the coupling of aromatic or heteroaromatic aldehydes with 2-aminophenol though the oxidative cyclization of the Schiffs' bases using 10 mol % of the Cu-nanoparticles in the presence of K_2CO_3 in MeOH. This method avoids the use of metal oxide or organic oxidizing agents, namely, DDQ or strong acids such as polyphosphoric acid or boric acid.
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In recent years, there has been growing interest in the catalytic properties of transition metal nanoparticles.[1] The high surface area-to-volume ratio of solid-supported metal nanoparticles[2] (1–10 nm in size) is mainly responsible for their catalytic properties and this can be exploited in many industrially important reactions.[3] Recent literature shows that the application of nanoparticles as catalysts in organic synthesis has been little explored. Cu-Nanoparticles, in particular, being cheap, require only mild reaction conditions for high yields of products in short reaction times as compared to traditional catalysts.

Benz-fused azoles are an important class of compounds and provide a common heterocyclic scaffold in biologically active and medicinally significant compounds.[4–9] Benzoxazoles are found in a variety of natural products[10] and are important targets in drug discovery[11] and also find applications in material science as photochromic agents[12] and laser dyes.[13]

The two most popular known strategies for synthesizing 2-substituted benzoxazoles are summarized in Scheme 1.

The literature methods are based on the approaches listed 'a' and 'b'. Route 'a' involves coupling a carbo-
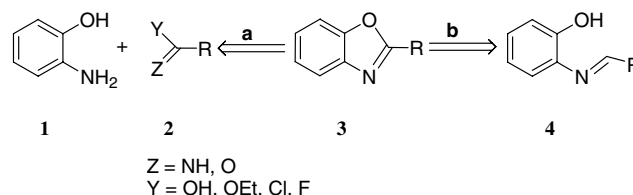
Scheme 1. Retrosynthesis of 2-substituted benzoxazoles.

xylic acid or its derivative with 2-aminophenol with dehydration catalyzed by strongly acidic conditions, for example, using boric or polyphosphoric acid and high reaction temperatures,[14] or using microwave-assisted reaction conditions.[15] The methodology developed under strategy '**b**' includes photochemical,[16] oxidative[17] and radical[18] cyclization of phenolic Schiffs' bases derived from the condensation of 2-aminophenols and aldehydes. In the latter reaction, various oxidants such as $PhI(OAc)_2$,[19] NiO_2,[20] $Ba(MnO_4)_2$,[21] DDQ,[22] $Mn(OAc)_2$,[23] $Pb(OAc)_2$[24] and $Th^-ClO_4^{+}$[25] have been used. Other methods include Ru-catalyzed hydroamination of diynes[26] with 2-aminophenols, degradative cyclization of imines derived from trifluoromethyl aryl ketones and 2-aminophenols under basic conditions[27] and CuI[28] catalyzed cyclization of *ortho*-haloanilides using 1,10-phenanthroline as the ligand in DME.

However, most of these methodologies suffer drawbacks such as lengthy procedures that require excess reagents (PPTS/PPA, *p*-TsOH, SOCl$_2$/HF, PPh$_3$-DEAD, metal catalyst/oxidizing agents), harsh reaction conditions

(strongly acidic, high temperature) and toxic solvents such as xylene and pyridine.[29] Oxidants are required in stoichiometric amounts relative to the substrate. Therefore, the development of a simple, efficient, inexpensive and nontoxic methodology is still needed for the synthesis of 2-arylbenzoxazoles.

As a part of continuing efforts in our laboratory towards the synthesis of bioactive compounds[30] and the use of nanoparticles[31] in new synthetic methodology, we report here on the synthesis of 2-arylbenzoxazoles using Cu-nanoparticles (Cu-np) as the catalyst.

The reduction of Cu^{2+} ions to Cu(0) in a reverse micellar system was employed to prepare the copper nanoparticles (Scheme 2).[32–34]

The sizes of Cu-nanoparticles prepared at $W_0 = 5$ (the water content parameter W_0 is defined as the molar ratio of water to surfactant concentration, $W_0 = [H_2O]/[surfactant]$) were confirmed as 10–17 nm through quasi elastic light scattering data (QELS) (Fig. 1a) and transmission electron microscopy (TEM) (Fig. 1b). Cu-Nanoparticles prepared were round in shape and brown in colour (colloidal state). The metallic nature of the Cu(0)-nanoparticles was confirmed by a characteristic UV absorption at λ 580 nm for the particles dispersed in cyclohexane.

Benzaldehyde was chosen as a representative aromatic aldehyde to optimize the reaction parameters. Thus, 1 mmol of 2-aminophenol was treated with varying

amounts of benzaldehyde using 2 equiv of K_2CO_3 as the base in the presence of 10 mol % of Cu-np in methanol. The best results were obtained on treating 1 mmol of 2-aminophenol with 1 mmol of benzaldehyde for 4 h (Scheme 3).[35]

To our delight, we observed the formation of 2-phenylbenzoxazole **3a** in a 90% yield after 4 h. Another set of control experiments was conducted without Cu-np which led to the formation of the Schiff's base. The isolated Schiffs' base was stirred with 10 mol % Cu-np in the presence of K_2CO_3, which resulted in the desired 2-phenylbenzoxazole **3a**. To focus on the mechanistic behaviour of Cu-np, a similar experiment was carried
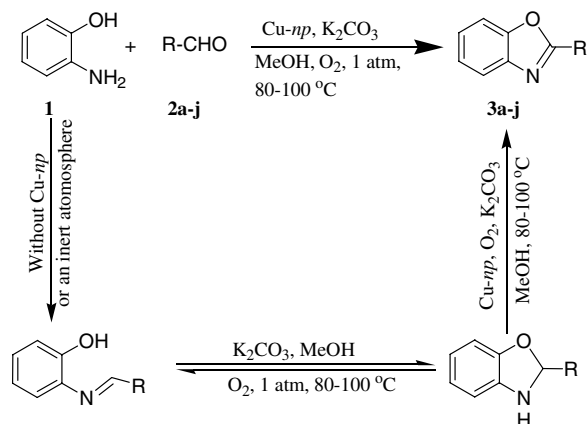
Scheme 3. Synthesis of a library of 2-arylbenzoxazoles.
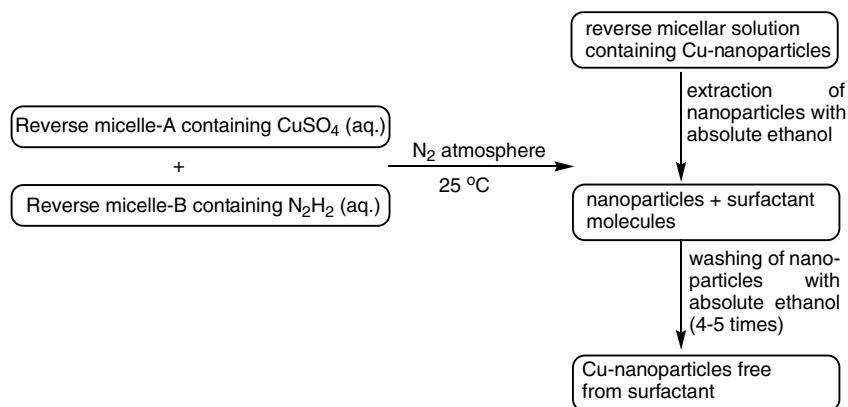
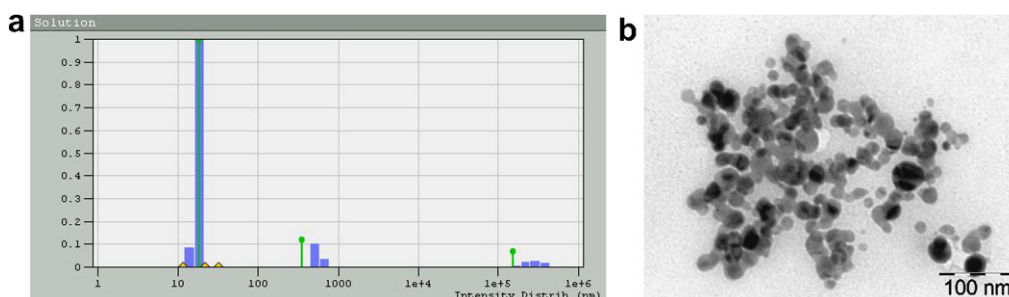**Scheme 2.** Preparation of Cu-nanoparticles.

Figure 1. (a) QELS data of Cu-nanoparticles: plot of percentile population distribution versus size distribution in nanometers (nm). (b) TEM image of the Cu-nanoparticles. The scale bar corresponds to 100 nm in the TEM image.

Table 1. Catalytic activity evaluation for the synthesis of 2-phenylbenzoxazole[a]

Entry	Cu-Nanoparticles (x mol %)	Time (h)	Yield[b] (%)
1	0	8.0	0
2	10	4.0	90
3	20	3.5	90
4	30	2.0	92
5	50	1.5	96

[a] Reaction conditions: 1.0 equiv of 2-aminophenol, 1.0 equiv of benzaldehyde, 2.0 equiv of K_2CO_3, x mol % Cu-np (18 ± 2 nm); solvent, MeOH; temperature, 80–100 °C; O_2; 1 atm.
[b] Isolated and unoptimized yields.

Table 2. Effect of size of the nanoparticles on the synthesis of 2-phenylbenzoxazole[a]

Entry	Cu-Nanoparticles (10 mol %, x ± 2 nm)	Time (h)	Yield[b] (%)
1	8	5.5	87
2	20	4.0	90
3	30	2.5	86
4	60	9.0	68
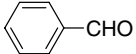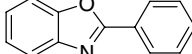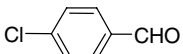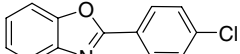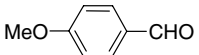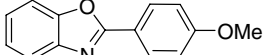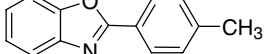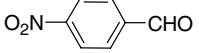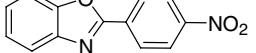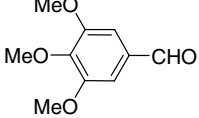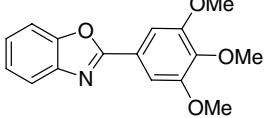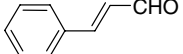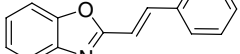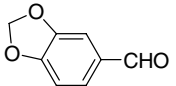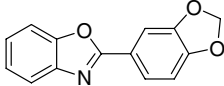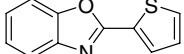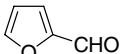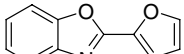
[a] Reaction conditions: 1.0 equiv of 2-aminophenol, 1.0 equiv of benzaldehyde, 2.0 equiv of K_2CO_3, 10 mol % Cu-np (x ± 2 nm); solvent, MeOH; temperature, 80–100 °C; O_2; 1 atm.
[b] Isolated and unoptimized yields.

out under an inert atmosphere, which resulted in the formation of the Schiffs' base. It was concluded that the condensation of 2-aminophenol with benzaldehyde in the presence of Cu-np generates the Schiffs' base

in situ which undergoes oxidative cyclization to give 2-phenylbenzoxazole. On each occasion, the reaction was monitored by thin layer chromatography.

With this positive result in hand further investigations were carried out to establish the optimum reaction

Table 3. Cu-Nanoparticle promoted synthesis of a library of arylbenzoxazoles[a]

Entry	Aldehyde		Product		Time (h)	Yield[b] (%)
1	**2a**		**3a**		3.0	90
2	**2b**		**3b**		4.7	87
3	**2c**		**3c**		3.6	92
4	**2d**		**3d**		4.5	83
5	**2e**		**3e**		4.6	75
6	**2f**		**3f**		1.5	95
7	**2g**		**3g**		3.2	86
8	**2h**		**3h**		3.0	74
9	**2i**		**3i**		4.8	69
10	**2j**		**3j**		5.0	71

[a] Reaction conditions: 1.0 equiv of 2-aminophenol, 1.0 equiv of aromatic/heteroaromatic aldehyde, 2.0 equiv of K_2CO_3, 10 mol % Cu-np (20 ± 2 nm); solvent, MeOH; temperature, 80–100 °C; O_2; 1 atm.
[b] Isolated and unoptimized yields.

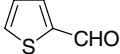conditions. Increasing the amount of Cu-np up to 50 mol % not only enhanced the product yields but also reduced the reaction time (Table 1).

In order to evaluate the efficacy of Cu-np as a catalyst, the reaction of 2-aminophenol with benzaldehyde was carried out in various solvents such as methanol, acetonitrile, toluene, dichloromethane and xylene. However, the only product obtained was 2-phenylbenzoxazole and methanol was the solvent of choice in terms of a 'cleaner' reaction medium since water was used for the work-up. The size of Cu-np plays an important role in terms of yields and reaction times. Changing the size of the particles resulted in a drop in the catalytic activity. Thus, the mechanism of the catalytic action of the nanoparticles was dependent on the size of Cu-np (Table 2).

The maximum reaction rate was observed for an average particle with a diameter of about 20 nm. A trend of decreasing reaction rate was found for the particles of less than 20 nm in diameter, while those above this diameter showed a steady decline in reaction rate with increasing size. It has been postulated that in the case of particles with average sizes less than 20 nm, a downward shift of the Fermi level takes place leading to an increase in the band gap energy. As a result, the particles require more energy to pump electrons to the adsorbed ions for electron transfer reactions. This leads to a reduction in the reaction rate when catalyzed by smaller particles. On the other hand, for nanoparticles >20 nm in diameter, the change of Fermi level is not appreciable. As these particles exhibit a smaller surface area for adsorption with increased particle size, a decrease in catalytic efficiency results.

Based on the above observations a range of aromatic and heteroaromatic aldehydes was subjected to the reaction with 2-aminophenol in the presence of 10 mol % of Cu-np of size 16 ± 2 nm. Both aromatic as well as heteroaromatic aldehydes reacted equally to give the products in excellent yields. Different substituents on the aryl group did not greatly effect the formation of the products (Table 3).

In summary, these results have demonstrated that Cu-np are efficient and mild catalysts for the synthesis of 2-arylbenzoxazoles via the condensation of aldehydes with 2-aminophenols. This direct synthesis includes in situ preparation of the Schiffs' bases, which undergo oxidative cyclization. Metal oxides, organic oxidizing agents or strong acids such as polyphosphoric acid are not required. In addition, our method is devoid of expensive reagents and high temperatures. Further investigations on synthetic applications and the mechanisms of the reactions of various metal nanoparticles are in progress and will be reported in due course.

Acknowledgement

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.09.066.

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35. A 50 ml round bottom flask was charged with 2-aminophenol **1** (1 mmol), the aromatic or heteroaromatic aldehyde **2**, (1 mmol), K_2CO_3 (2 mmol) and Cu-nanoparticles (10 mol %, 16 ± 2 nm in size), followed by 10 ml methanol. The resulting solution was refluxed at 100 °C for the appropriate time mentioned in Table 3. The extent of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with distilled water (2×10 ml) and the 2-arylbenzoxazole extracted with ethyl acetate (2×15 ml). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed in vacuo. The crude product was subjected to purification by silica gel column chromatography using 20% ethyl acetate in petroleum ether as an eluent to yield the 2-arylbenzoxazole **3a–j**. The structures of all the products were unambiguously established on the basis of their spectral analysis (IR, ^{1}H, ^{13}C NMR and mass spectral data). All the products are known compounds. (See Supplementary data.)