



Novel one-pot Cu-nanoparticles-catalyzed Mannich reaction

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ABSTRACT

Recyclable heterogeneous Cu-nanoparticles efficiently catalyzed the one-pot three-component Mannich reaction of ketones, aromatic aldehydes and amines in methanol. This method provides a novel and improved method for obtaining β-amino carbonyl compounds in terms of good yield with little catalyst loading.

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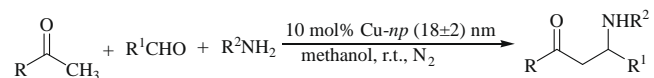
The vast majority of nature's molecules including proteins, nucleic acids and most biologically active compounds contain nitrogen. Consequently, developing new synthetic methods for the construction of nitrogenous molecules¹ has defined the frontiers of organic synthesis since its very beginning. The Mannich reaction is a very useful platform for the development of several molecules.² Originally, this reaction produces β-amino carbonyl compounds from three components such as an amine, aldehyde and ketone. The products of the Mannich reaction are used for the synthesis of amino alcohols, peptides and lactams and as precursors to synthesize amino acids. Moreover, three-component coupling Mannich reactions are the most important in organic synthesis³ and are conventionally used for making synthetic intermediates, as several elements can be introduced in a single step into a molecule. The Mannich reaction relies on two as well as three component systems, but the preferable route is the use of a one-pot three-component setup rather than a two step.⁴

Numerous versions of the Mannich reaction have been developed⁵ in the past. Conventional catalysts for the classical Mannich reaction⁶ of aldehydes, ketone and amines involve mainly Lewis acids,^{7–9} Bronsted acids^{10–12} and Lewis base catalysis.¹³ However, sodium tetrakis (3,5-trifluoromethylphenyl)borate,¹⁴ scandium tris (dodecanesulfonate),¹⁵ organometallic,¹⁶ ionic liquids^{17,18} and recently NbCl₅¹⁹ have also been found to catalyze this reaction. These catalysts suffer mainly from the drawbacks of long reaction time, toxicity and their usage in stoichiometric amounts. While searching for economical, cheap and better catalysts, we thought

it worthwhile to perform a controlled reaction condition for the Mannich reaction using nanoparticles.

Nanoparticles are core base materials for implementing nanotechnology and have attracted researchers in the field of chemistry because of their current promising applications in organic synthesis.^{20–24} Metal-nanoparticles have a characteristic high surface-to-volume ratio that translates into more active sites per unit area compared to standard catalysts. Cu-nanoparticles, in particular, are cheap and easy to make and require mild reaction conditions for high yield products in comparison to traditional catalysts.^{25,26} Cu-nanoparticles in comparison to homogeneous copper catalysts have the advantage of recyclability with greater ease of reaction selectivity, and thus behave as efficient heterogeneous catalysts. In continuation of our efforts towards the development of newer synthetic methodologies²⁷ for organic transformations using transition metal nanoparticles,^{25,26,28} we report herein an efficient and recyclable Cu-nanoparticle (Cu-nps)-catalyzed one pot three-component Mannich reaction using aldehydes, ketones and amines.

To examine the catalytic behaviour of Cu-nanoparticles in the Mannich reaction, benzaldehyde (1 mmol), aniline (1 mmol) and acetophenone (1 mmol) in methanol (5 ml) were stirred under a nitrogen atmosphere at room temperature in the presence of 10 mol % of Cu-nanoparticles for 8–12 h (Scheme 1),²⁹ and the reaction yielded 98% β-amino ketone. The structure was elucidated on the basis of spectral data.



Scheme 1. Cu-nanoparticles-catalyzed Mannich reaction of acetophenone, benzaldehyde and aniline.

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We chose various metal nanoparticles, namely, Cu, Au and Ni-*np* to optimize catalytic activity under similar reaction conditions in the Mannich reaction, and on the basis of product formation we found that Cu-*np* was efficacious in comparison to Au or Ni-*np* in the Mannich reaction.

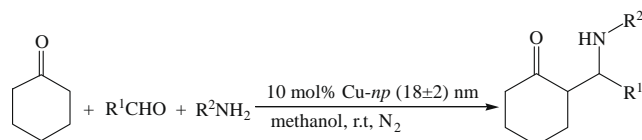
A control experiment was conducted in the absence of Cu-*np*. The reaction did not proceed and the substrate remained unchanged. Mechanistically, the reaction proceeds typically via imine formation through the condensation of aldehyde and amine, followed by the attack of an enol form of ketone on imine to afford the desired product in good yield.

Encouraged by these remarkable results, we screened a variety of aromatic aldehydes and amines including electron-withdrawing and electron-donating groups. When *ortho*-substituted anilines were used as substrates, the reaction gave no product due to the steric hindrance of *ortho*-substituents. In the investigation of various benzaldehydes, it was found that *p*-methylbenzaldehyde is most active in the reaction (Table 1, entry 5). This is because the substituents on benzaldehyde have a remarkable influence on the stability of intermediate 'RC₆H₄C⁺HNHC₆H₅' derived from the aldehyde and the amine. The rich electron-donating substituents such as '-OCH₃' result in low stability of the intermediate (Table 1, entries 9, 12 and 18). However, electron-withdrawing groups such as '-NO₂' degrade the activity of the intermediate and result in a very low amount of yield (Table 1, entries 7 and 10). In addition, aliphatic aldehydes, such as isobutyraldehyde, do not favour the formation of the desired product due to enamine formation.

In order to ascertain the scope and limitation of this Cu-nanoparticle-catalyzed Mannich reaction, we extended the use of the catalytic systems to the reaction of cyclohexanone with various aldehydes and amines (Scheme 2, Table 1). Better results were obtained for the formation of β-amino ketones.²⁹

In addition, to compare the catalytic activity of Cu-nanoparticles, the reaction was also tried with copper salts (such as CuCl₂ and CuSO₄) and was found to be unsuccessful under similar conditions.

Catalyst concentration plays a major role in the optimization of the product yield. By increasing the molar concentration of Cu-*np* (18 ± 2) nm from 10 to 50 mol %, it was observed that increased loading of the catalyst from 10 to 50 mol % gave almost the same yield of the product (Table 2). It appears that a concentration of 10 mol % of Cu-nanoparticles is the suitable choice for an optimum yield of β-amino ketones.



Scheme 2. Cu-nanoparticle-catalyzed Mannich reaction of cyclohexanone, benzaldehyde and aniline.

Table 2

Optimization of the concentration of Cu-nanoparticles in the Mannich reaction^a

Entry	Cu- <i>np</i> (18 ± 2 nm)/mol %	Time/h	Yield ^b (%)
1	0	42	0
2	10	8	93
3	30	8	96
4	50	8	97

^a Reaction conditions: acetophenone (1 mmol), benzaldehyde (1 mmol) and aniline (1 mmol), × mol % Cu-*np* (18 ± 2) nm; solvent methanol; rt, N₂ atmosphere.

^b Isolated and unoptimized yields.

In addition, an increase in the concentration of Cu-nanoparticles also resulted in the oxidation of Cu-nanoparticles to CuO during the recycling of the catalyst. We surmised that the oxidized CuO underwent conglomeration, thus reducing the surface area of the nanoparticles and hence resulting in a decrease in catalytic activity during recycling.

Cu-nanoparticles were prepared by the reverse micellar drop-lets method^{28d,30} and the size was confirmed as 10–80 nm through quasi-elastic light scattering data (QELS) (Fig. 1a) and transmission electron microscopy (TEM) (Fig. 1b).

The study shows that the catalytic effect of nanoparticles is dependent on the size of nanoparticles (Table 3). The maximum reaction rate has been observed for an average particle of diameter of about 20 nm. Particles below this size tended to show a decrease in reaction rate with a decrease in particle size, while those above this diameter showed a steady decline in the reaction rate with increasing size. It has been postulated that in the case of particles with a size less than 20 nm, a downward shift of the Fermi level takes place with a consequent increase of band gap energy.³¹ As a result, the particles require more energy to pump electrons to the adsorbed ions in the electron transfer reaction. This leads to a reduction in reaction rate when catalyzed by smaller particles.

Table 1

One-pot three component Mannich reaction of ketones, aromatic aldehydes and aromatic amines^a

Entry	Ketone	R ¹	R ²	Time (h)	Yield ^b (%)	Mp (°C)
1	Acetophenone	Ph	Ph	8	93	169–171
2	Acetophenone	Ph	4-CH ₃ C ₆ H ₄	9	97	170–171
3	Acetophenone	Ph	3,4-(CH ₃) ₂ C ₆ H ₃	10.5	92	145–146
4	Acetophenone	Ph	4-ClC ₆ H ₄	9	95	172–173
5	Acetophenone	4-CH ₃ C ₆ H ₄	Ph	8	97	129–130
6	Acetophenone	Ph	4-OCH ₃ C ₆ H ₄	10	91	163–164
7	Acetophenone	Ph	4-NO ₂ C ₆ H ₄	12	73	185–186
8	Acetophenone	Ph	4-IC ₆ H ₄	9	89	168–170
9	Acetophenone	4-OCH ₃ C ₆ H ₄	Ph	9	91	150–152
10	Acetophenone	4-NO ₂ C ₆ H ₄	Ph	12	74	105–106
11	Acetophenone	4-ClC ₆ H ₄	Ph	12	91	117–118
12	Acetophenone	4-OCH ₃ C ₆ H ₄	4-IC ₆ H ₄	9.5	76	173–175
13	<i>p</i> -methylacetophenone	Ph	Ph	10	85	137–138
14	<i>p</i> -nitroacetophenone	Ph	Ph	10	87	146–147
15	Cyclohexanone	Ph	Ph	9	88	139–140
16	Cyclohexanone	Ph	4-CH ₃ C ₆ H ₄	11	90	118–119
17	Cyclohexanone	Ph	4-ClC ₆ H ₄	12	91	137–138
18	Cyclohexanone	4-OCH ₃ C ₆ H ₄	Ph	12	83	132–133

^a Reaction conditions: acetophenone (1 mmol)/cyclohexanone, aromatic aldehydes (1 mmol) and aromatic amines (1 mmol), 10 mol % Cu-*np* (18 ± 2) nm; solvent methanol; rt, N₂ atmosphere.

^b Isolated and unoptimized yields.

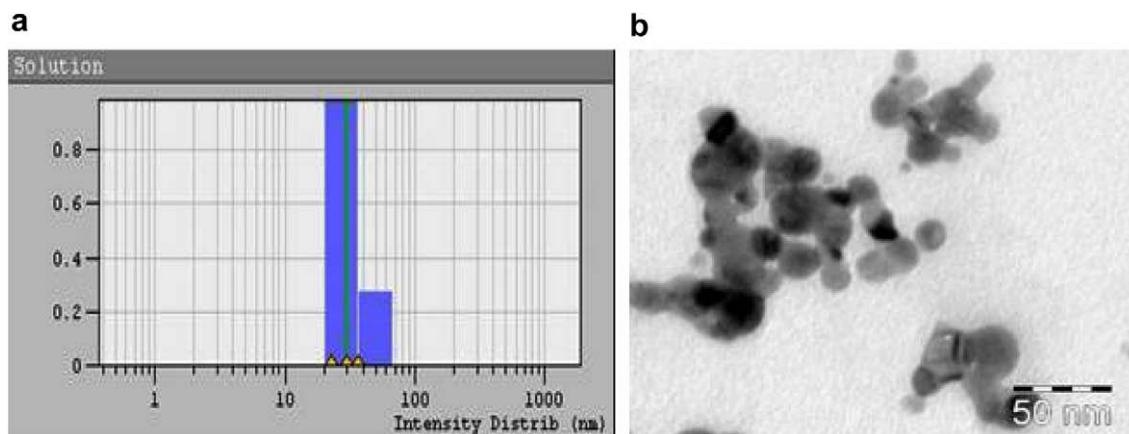


Figure 1. (a) QELS data of Cu-nanoparticles: Plot of population distribution in percentile versus size distribution in nanometres (nm); (b) TEM image of Cu-nanoparticles.

Table 3
Size screening of Cu-nanoparticles on three-component Mannich reaction^a

Entry	Particle size (± 2) nm	Time (h)	Yield ^b (%)
1	10	8	87
2	20	8	95
3	30	8	84
4	50	8	71
5	70	8	65

^a Reaction conditions: acetophenone (1 mmol), benzaldehyde (1 mmol) and aniline (1 mmol), 10 mol % Cu-*np* (± 2) nm; solvent methanol; rt, N₂ atmosphere.

Table 4
Recycling yields

No. of cycles ^a	Fresh	Run 1	Run 2	Run 3	Run 4
Yield (%) ^b	93	85	80	71	62
Time (h)	8	8	8	8	8

^a Reaction conditions: acetophenone (1 mmol), benzaldehyde (1 mmol) and aniline (1 mmol), 10 mol % Cu-*np* (18 ± 2) nm; solvent methanol; rt, N₂ atmosphere.

^b Isolated and unoptimized yields.

On the other hand, for nanoparticles with diameters above 20 nm, the change of the Fermi level is not significant. As these particles exhibit less surface area for adsorption with increased particle size, a decrease in catalytic efficiency results.

The nature of reaction media has an important role in the three-component Mannich reaction in the presence of Cu-nanoparticles (10 mol %). Here, initially, we chose water as a solvent that had been conventionally reported but we found that the Cu-nanoparticles are easily oxidized in the water and are not recyclable. We thus chose methanol as a solvent which gives excellent results and in which Cu-nanoparticles are recyclable.

We found that the Cu-nanoparticles could be recycled and reused three to four times by separating them from the reaction mixture through centrifugation at 2000–3000 rpm at 10 °C for 5–8 min and by frequent washing with THF. They could be reused as catalysts and this results in the formation of **1** (Table 1) from 85% to 62% yield (Table 4, run 1–3). The change in their catalytic activity was monitored. The relation between the number of cycles of the reaction and the catalytic activity in terms of yields is presented in Figure 2. The data shows a gradual loss of the activity of the catalyst used in the experiment with an increasing number of cycles. Only a mild decrease in reaction yields in the second cycle was observed, but there was a gradual decrease in the yield of the product after the third and fourth cycle. One explanation could be that the active catalyst is efficiently recycled but is of limited stability. This causes the size of the particles to increase dramatically and hence

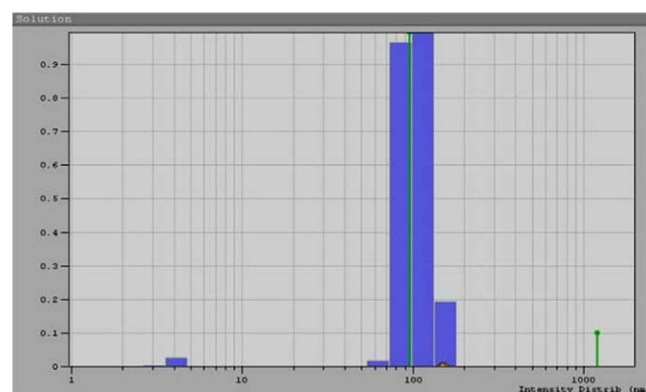


Figure 2. QELS data of recycled Cu-nanoparticles: plot of population distribution in percentile versus size distribution in nanometres (nm).

catalytic activity decreases with a decrease in the surface area of the particles. It was observed that when the number of cycles of the reaction increased, the catalytic activity of the Cu-nanoparticle decreased (Table 4). Another explanation is that catalyst recycling is not as efficient as anticipated because of the slow oxidation of the Cu-nanoparticles.

Overall, this methodology offers the competitive advantages of recyclability of the catalyst which could be used without further purification and without any additives. It also requires less loading of the catalyst and has broad substrate applicability with ease and improved yields.

In conclusion, we have successfully developed a novel, easy, economic and practical method for the synthesis of β -amino ketones. The catalyst can be recovered and reused, thus making this procedure more environmentally acceptable. In addition, our method does not use expensive reagents or high temperatures. Further investigations on the synthetic applications of various metal-nanoparticles are in progress and will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.031.

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29. *General procedure for the preparation of β -amino carbonyls*: In a 50 ml round bottom flask, acetophenone (1 mmol)/cyclohexanone, aromatic aldehydes (1 mmol) and aromatic amines (1 mmol) in methanol (4 ml) were mixed and stirred under a nitrogen atmosphere at room temperature. To this, Cu-nanoparticle (10 mol % 18 ± 2 nm) were added. On completion of the reaction (as monitored by TLC using Petroleum Ether/ACOEt = 80:20 as an eluent), the solid product was filtered and washed with methanol. The precipitate was dissolved in chloroform to isolate the Cu-nanoparticle via centrifugation at 2000–3000 rpm, at 10 °C for 5 min. The chloroform was removed under reduced pressure. The crude product was subjected to purification by recrystallization using Ethanol or flash chromatography using 15% ethyl acetate, 5% methanol and 80% petroleum ether as an eluent to yield the β -amino carbonyls **1–18**. The structures of all the products were unambiguously established on the basis of their spectral analysis (IR, ¹H NMR, ¹³C NMR and GC–MS mass spectral data). All the products are known compounds (see Supplementary data).
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