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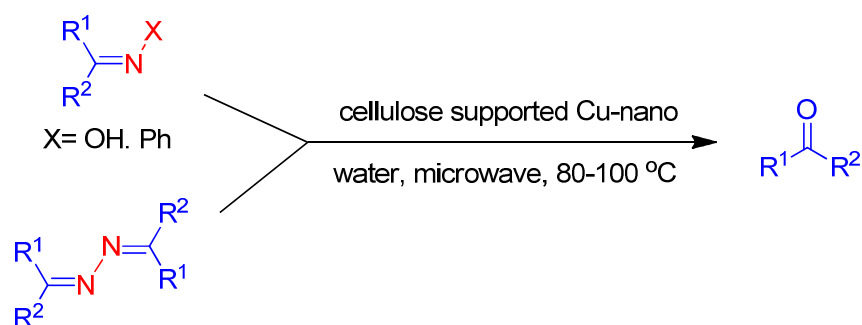
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Graphical abstract

Deprotection of oximes, imines, and azines to the corresponding carbonyls using Cu-nano particles on cellulose template as green reusable catalyst

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Cellulose supported Cu-nano particles efficiently catalyze the deprotection of oximes, imines, and azines in water under neutral condition.

Deprotection of oximes, imines, and azines to the corresponding carbonyls using Cu-nano particles on cellulose template as green reusable catalyst†

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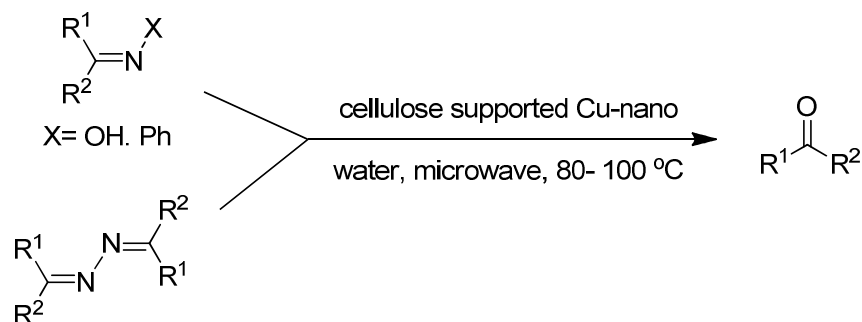
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†Electronic supplementary information (ESI) available: Experimental section, characterization of all compounds, and copies of NMR spectra.

Key Words: Nano particles, Green chemistry, Cellulose template, Microwave synthesis, Carbonyl deprotection

Abstract: Deprotection of wide varieties of oximes, imines, and azines to the corresponding carbonyls have been achieved using Cu-nano particles on cellulose template as reusable catalyst. The reactions were carried out at 80-100 °C using microwave irradiation in water under neutral condition. The catalyst can be reused for several cycles with good to excellent yield.



Protection-deprotection of functional group is a very common and widely used technique in organic synthesis.¹ Generally sensitive functional groups are needed to be protected to have a better control over the chemistry during a multistep reaction sequence. In many cases the protecting groups also show activating and directing properties.² Oximes, imines, azines are frequently used protecting groups for carbonyls because they provide relatively stable compounds compared to others. These compounds can also be prepared from the sources other than carbonyls like alcohols,³ amines,⁴ nitriles,⁵ nitroalkanes,⁶ azaarenes⁷ etc. which sometime open up newer synthetic avenues for the selective insertion of aldehydes and ketones. There are number of methodologies reported for the deprotection of oximes and related compounds.^{1,8} The classical method for the cleavage of oximes to carbonyls is acid hydrolysis,⁹ although other many reagents like, pyridinium chlorochromate (PCC) and related Cr(VI) compounds,¹⁰ KMnO₄/Alumina,¹¹ trimethylphosphine and 2,2'-dipyridyl diselenide,¹² vanadomolybdophosphate (H₆PMo₉V₃O₄₀),¹³ mixed metal oxide CeO₂-ZrO₂,¹⁴ FeCl₃/TEMPO,¹⁵ Iron(III) porphyrin complex,¹⁶ gaseous NO₂,¹⁷ Cu(I) chloride/kieselghur,¹⁸ CuCl₂·2H₂O,¹⁹ Mixed (Fe²⁺ and Cu²⁺) double metal hexacyanocobaltates,²⁰ Platinum(II) terpyridyl acetylide complex/O₂/hv,²¹ TiO₂/mesoporous silica,²² Cobalt(II) phthalocyanine/ionic liquid,²³ Au/CeO₂,²⁴ I₂/water,²⁵ 2-nitro-4,5-dichloropyridazin-3(2*H*)-one,²⁶ NaNO₂,²⁷ etc. are also reported. Most of these methods are quite efficient and good yielding, however, they suffer from one or more serious drawbacks (Table 1) like, use of strong Lewis and Bronsted acids,⁹ use of costly and hazardous metal/ligands (i.e., Mn, Cr, Ti, Au, Pt),^{10-16,20-24} use of toxic solvents, difficulty in catalyst/product separation, problems associated with waste disposal, necessity of robust reaction conditions, generation of over-oxidized products, long reaction time etc. Also, many of the catalysts are homogeneous and thus cannot be recycled.²⁵⁻²⁷ In this situation, development of an efficient, re-usable heterogeneous catalyst which can deprotect oximes, imines, and azines in water under neutral condition can be considered as highly useful.

Table 1. Advantages of the cellulose supported Cu-nano particles compared to the reported ones

Sl. No.	Reagents	Advantage/disadvantage
1	Acid hydrolysis	Use of strong Bronsted or Lewis acid

2	Pyridinium chlorochromate (PCC) and related Cr(VI) compounds ¹⁰	Use of toxic Chromium(VI) reagents
3	KMnO ₄ /Alumina	Accumulation of manganese dioxide and lack of catalyst recyclability
4	Trimethylphosphine and 2,2'-dipyridyl diselenide ¹²	Use of toxic and costly reagents and metals
5	FeCl ₃ /TEMPO ¹⁵	Use of costly reagents and lack of catalyst recyclability
6	Gaseous NO ₂ ¹⁷	Use of corrosive and extreme reaction conditions
7	CuCl ₂ .2H ₂ O ¹⁹	Lack of catalyst recyclability
8	Platinum(II) terpyridyl acetylide complex/O ₂ /hv ²²	Use of costly reagents
9	Au/CeO ₂ ²⁴	Use of costly reagents
10	I ₂ /water ²⁵	Lack of catalyst recyclability
11	2-Nitro-4,5-dichloropyridazin-3(2 <i>H</i>)-one ²⁶	Lack of catalyst recyclability
12	NaNO ₂ ²⁷	Lack of catalyst recyclability
13	Cellulose supported Cu-nano particles	Cost-effective, Re-usable heterogeneous catalyst. Works in a comparatively milder reaction condition under microwave heating

Stabilization of metal nano particles using biopolymers like cellulose in place of synthetic polymers is currently getting lot of importance because of possible environmental benefit.²⁸ Cellulose consists of anhydroglucose units joined by oxygen linkage (β -1-4 glucosidic bond) which forms a molecular chain. As a whole, the structure creates microfibrils up to 30 nm width that are three dimensionally connected to each other.²⁹ Because of the strong electrostatic ion

dipole interaction, the metal nano particles are stabilized in those microfibrils. Also, depending upon the different porosity of the microfibril templates, the shape and size of those nanoparticles are varied.³⁰ Although various properties of cellulose supported metal nano particles have been studied, their potential applications as renewable heterogeneous catalyst have not been widely explored, so far. In this context, herein, we report application of cellulose supported Cu-nano particles as renewable green catalyst for the efficient deprotection of C=N bonds of oximes, imines and azines to the corresponding carbonyls.

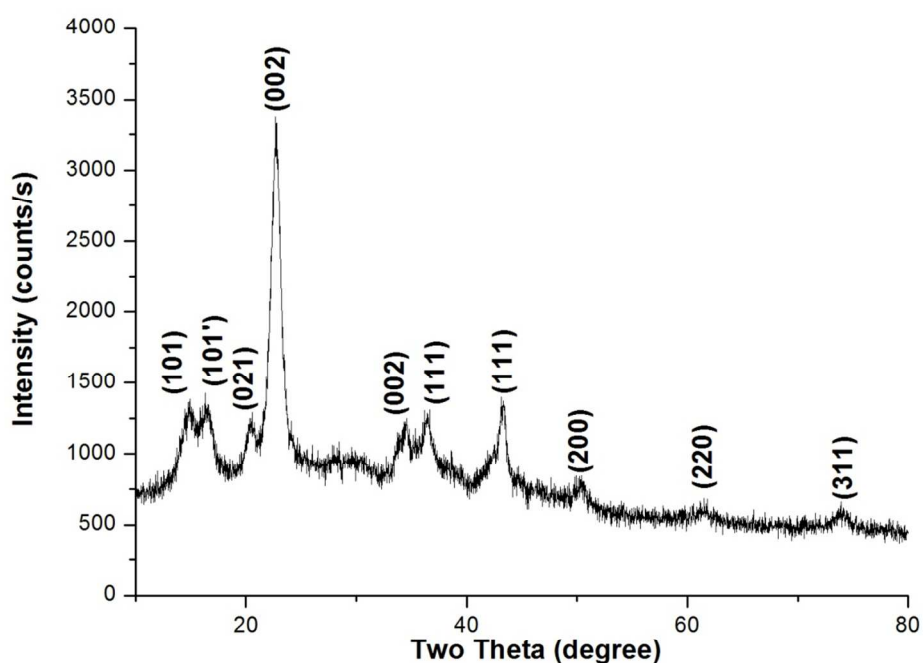


Figure 1. XRD spectra of Cu-nano particles on nano porous cellulose template

In continuation of our on-going work on nano materials,³¹ we were interested to study the catalytic properties of cellulose supported Cu-nano particles. Usually the cellulose supported Cu-nano particles are prepared by reducing Cu(II) on cellulose surface using sodium borohydride.³² We have also prepared the nano particles using hydrazine hydrate/NaOH as reducing agent in place of NaBH₄. It was found that reduction of Cu(II) acetate on cellulose using either of the process provided stable black colored Cu-cellulose mixture. Initial powder X-ray diffraction study (XRD) showed that in combination with four cellulose peaks at 2 θ values 14.8°, 16.4°,

20.4°, and 22.9°, corresponding to the Bragg planes (101), (101'), (021), (002), there were four peaks at 2θ values of 34.4°, 36.3°, 61.4° and 74.1° corresponding to (002), (111), (220) and (311) planes representing Cu₂O and another two distinguished peaks at 2θ values of 43.2° and 50.4° corresponding to (111) and (200) planes representing Cu(0) (Figure 1). No peaks corresponding to Cu(II) or any other impurity was observed which confirmed the existence of only Cu(0) and Cu(I). The TEM study showed that the size of the metal particles were in the range of 2-10 nm with the average size of 6 nm (Figure 2). The high resolution TEM identified the reticular lattice planes inside the nano particles indicating crystalline nature.

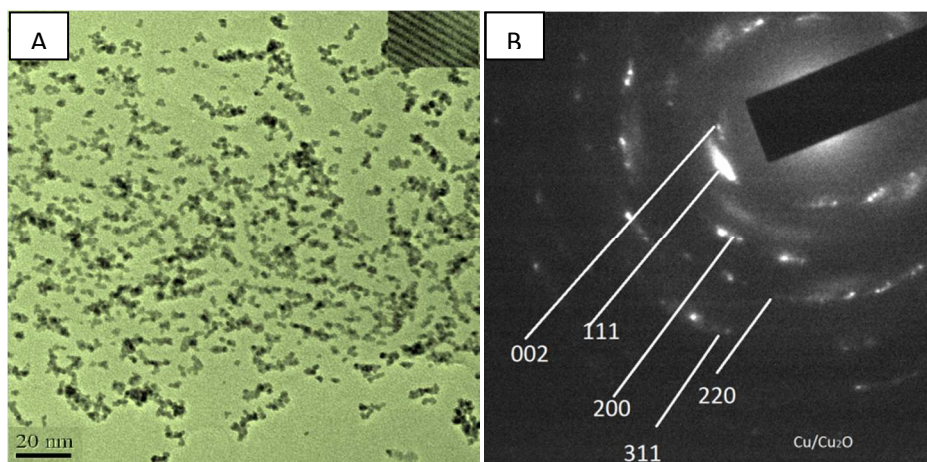
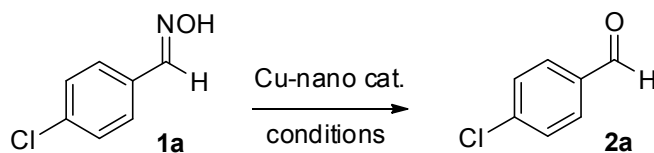


Figure 2. (A) TEM and HRTEM (inset) images of the Cu(0)/Cu₂O nano- particles on cellulose template. (B) Location of selected area electron diffraction (SAED) pattern.

Table 2. Optimization of the reaction condition



Entry	Catalyst loading ^a	Heating condition	Solvent	Temperature	Time	Yield (%) ^b
1	Stoichiometric	Normal heating	CH ₃ CN	100 °C	48 h	40
2	No catalyst	Normal heating	CH ₃ CN	100 °C	48 h	0

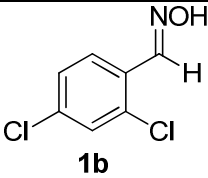
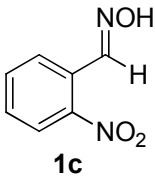
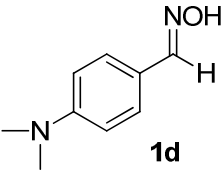
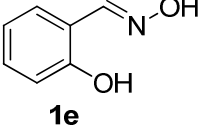
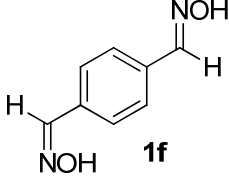
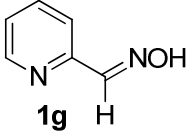
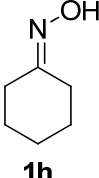
3	Stoichiometric	Microwave heating	CH ₃ CN	140 °C	5 min	89
4	No catalyst	Microwave heating	CH ₃ CN	140 °C	10 min	0
5	20 mol%	Microwave heating	CH ₃ CN	140 °C	5 min	89
6	20 mol%	Microwave heating	CH ₃ CN	80 °C	5 min	89
7	20 mol%	Microwave heating	H₂O	80 °C	5 min	89

^aReactions are carried out using 1 mmol substrate. ^bYields refer to isolated yield.

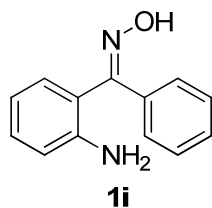
To find out the catalytic properties of the prepared Cu-nano particles, deoxygenation of 4-chlorobenzaldehyde oxime (**1a**) was studied. Refluxing a mixture of **1a** and Cu-nano catalyst in acetonitrile provided the corresponding aldehyde **2a**, but the yield was low and also reaction time was very long (Entry 1, Table 2). Influenced by the reports of dramatic reaction rate acceleration and yield improvement by the microwave irradiation, it was decided to carry out the reaction under microwave.³³ So, the same reaction was repeated under microwave irradiation in a sealed vial, which provided a reasonably good yield of the product **2a** in very less time (Entry 3, Table 2). The requirement of the metal nano particles in the reaction was established by performing two blank reactions where substrate was heated in the absence of catalyst (Entry 2 and 4, Table 2). Both the reactions failed to provide any isolable product. It was observed that only catalytic amount of nano particle was sufficient to carry out the reaction and also water could effectively be used as solvent. Under optimized reaction condition, a mixture of **1a** and catalytic amount of Cu-nano particle was heated under microwave irradiation in a closed vial at 80 °C for 5 minutes (Entry 7, Table 2). To widen the scope of the reaction, different aromatic and heterocyclic oximes were tested (Table 3). In all the cases the reaction went on smoothly to produce corresponding carbonyls. Although the rate of the reactions did not change significantly, the yields somehow varied with the substituents present in the compounds. The electron donating substituents like –OH, –NMe₂, NH₂ etc. led to comparatively lower yield of the products. The catalyst was equally effective to both the aldoximes and ketoximes. All the products were well characterized by

comparison of the physical characteristics (TLC R_f value, melting point) and spectral data (IR and NMR) with those of the authentic samples.

Table 3. Deprotection of oximes^a

Entries	Oximes	Temperature (°C)/ time (min)	Yield (%) ^b
1	 1b	80/ 5	87
2	 1c	80/ 5	88
3	 1d	100/ 8	75
4	 1e	100/ 8	77
5	 1f	100/ 8	85
6	 1g	80/ 5	79
7	 1h	100/5	70

8



100/ 8

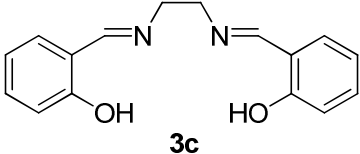
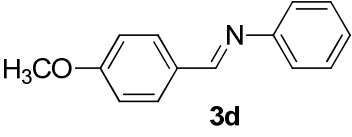
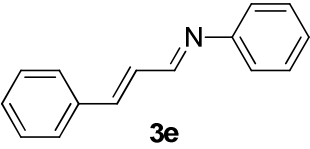
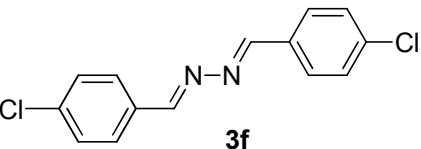
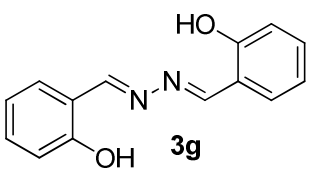
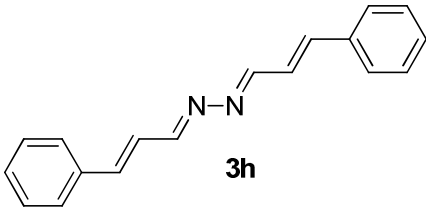
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^aReaction conditions: Mixture of oxime (1 mmol), Cu-nano catalyst (20 mol%), and H₂O (5 mL) was heated in a sealed microwave vial at given temperature for the stipulated time. ^bYields refer to isolated yield of the carbonyls.

After successful experiment with oximes, deprotection of imines and azines were studied. It was observed that the catalyst was also able to efficiently cleave imines and azines to the corresponding amines and carbonyls (Table 4). A number of different imines and azines were deprotected using the standardized reaction condition. In this case also the yield varied with the nature of the substituents. In any of the reactions no formation of over oxidized products like acid or acid decarboxylated compounds were observed. Different sensitive functional groups like hydroxyl, alkene etc. were well tolerated in the reaction condition. All the products were well characterized by co-TLC expression and comparison of melting point, IR, and NMR data with the corresponding carbonyls. To check the recyclability, the catalyst was filtered after the reaction and reused up to 4 times without a major loss of catalytic activity (Figure 3).

Table 4. Deprotection of imines and azines^a

Entries	Imines and azines	Temperature (°C), time (min)	Yield (%) ^b
1	<p style="text-align: center;">3a</p>	80/ 5	88
2	<p style="text-align: center;">3b</p>	100/ 8	74

3	 3c	100/8	72
4	 3d	100/ 5	75
5	 3e	100/ 8	82
6	 3f	80/ 8	87
7	 3g	100/7	76
8	 3h	100/8	83

^aReaction condition: Mixture of imines/azines (1 mmol), Cu-nano catalyst (20 mol%), and H₂O (5 mL) was heated in a sealed microwave vial at given temperature for the stipulated time.

^bYields refer to isolated yield of the carbonyls.

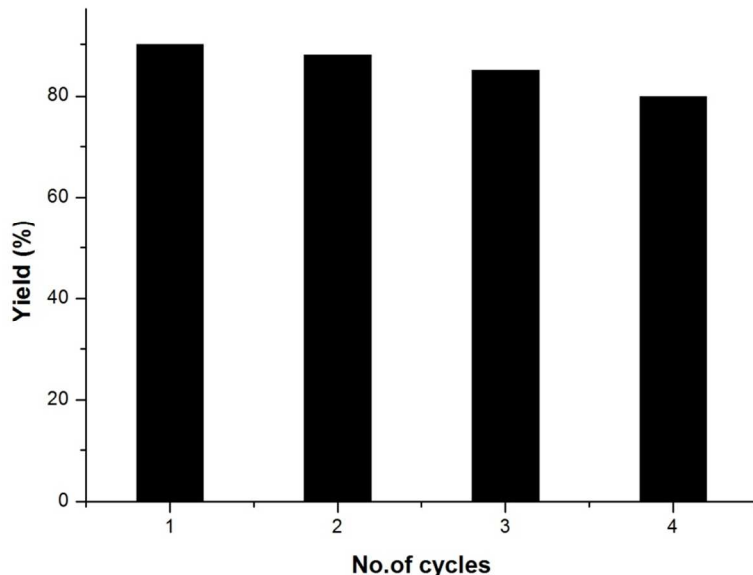
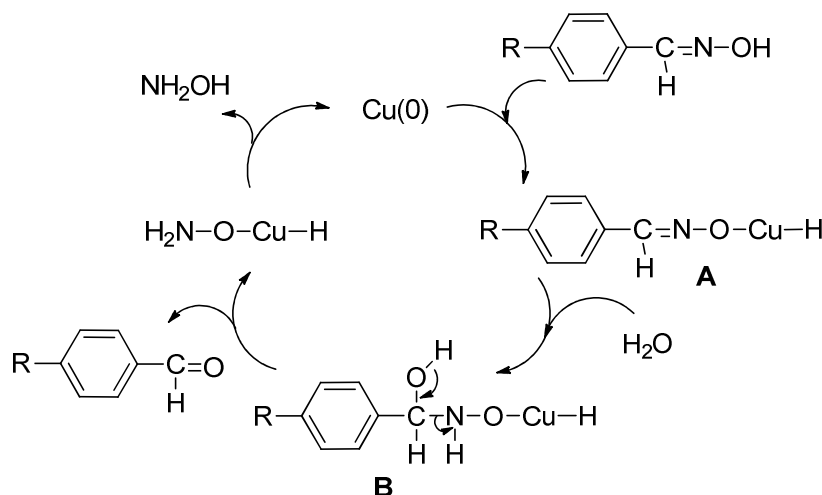


Figure 3: Study of the catalyst recyclability for the deoximation of *p*-chlorobenzaldehyde oxime (**1a**)

There are two different mechanisms reported for Cu-catalyzed deprotection of oximes, imines, and azines.^{18,19} While oxidative deoximation is proposed for Cu(I) promoted reactions,¹⁸ in case of Cu(II)¹⁹ it is merely a co-ordination with nitrogen which increases the polarity of the C=N and leads to nucleophilic attack by water. In the current catalytic system there is a mixture of Cu(0) and Cu(I). To test the possibility of the oxidative deoximation, an experiment was carried out under strictly inert atmosphere. It was observed that the reaction was equally effective under inert atmosphere also. In this situation, co-ordination of Cu(0)/Cu(I) with nitrogen of C=N is a very likely mechanism for the deprotection of oximes, imines, and azines. An alternative mechanism may also be possible for oximes only. It starts with the oxidative insertion of Cu(0) in the oximes to produce an intermediate **A** (Scheme 1). Subsequent, nucleophilic attack of water cleaves the C=N via intermediate **B** releasing the carbonyls.



Scheme 1. A plausible mechanism for the deoxygenation using Cu(0).

In conclusion, cellulose supported Cu-nano particles were shown to be an effective heterogeneous catalyst which can deprotect oximes, imines, and azines to the corresponding carbonyls and amines. The superiority of the catalytic system over the other existing reactions can be described by the few salient features like, neutral reaction condition, ability to perform the reaction in water, very short reaction time, no use of any expensive reagents or ligands, recyclability of the catalyst, clean reaction profile etc. Application of the catalytic system towards more complex substrates and different reactions are going on.

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