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

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The deprotection of wide varieties of oximes, imines, and azines to their corresponding carbonyls has been achieved using Cu-nanoparticles on a cellulose template as a 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.

The protection–deprotection of functional group is a very common and widely used technique in organic synthesis.[1] Generally, sensitive functional groups need 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, and azines are frequently used as 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, such as alcohols,[3] amines,[4] nitriles,[5] nitroalkanes,[6] and azaarenes,[7] which sometimes provide newer synthetic avenues for the selective insertion of aldehydes and ketones. There are numerous 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 many other reagents, such as pyridinium chlorochromate (PCC) and related Cr(VI) compounds,[10] KMnO₄/alumina,[11] trimethylphosphine and 2,2′-dipyridyl diselenide,[12] vanadomolybdophosphate ($H_6PMo_9V_3O_{40}$),[13] mixed metal oxide CeO_2–ZrO_2,[14] FeCl₃/TEMPO,[15] iron(III) porphyrin complex,[16] gaseous NO_2,[17] Cu(I) chloride/kieselghur,[18] CuCl₂, 2H₂O,[19] mixed (Fe^{2+} and Cu^{2+}) double metal hexacyanocobaltates,[20]

platinum(II) terpyridyl acetylide complex/O₂/hν,[21] TiO₂/mesoporous silica,[22] cobalt(II) phthalocyanine/ionic liquid,[23] Au/CeO₂,[24] I₂/water,[25] 2-nitro-4,5-dichloropyridazin-3(2H)-one,[26] and NaNO₂,[27] have been also reported. Most of these methods are considerably efficient and produce good yields; however, they suffer from one or more serious drawbacks (Table 1), such as requiring the use of strong Lewis and Bronsted acids,[9] use of costly and hazardous metal/ligands (*i.e.*, Mn, Cr, Ti, Au,

Table 1 Advantages of cellulose supported Cu-nano catalysts over the previously 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	KMnO₄/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	FeCl₃/TEMPO[15]	Use of costly reagents and lack of catalyst recyclability
6	Gaseous NO₂ (ref. 17)	Use of corrosive and extreme reaction conditions
7	CuCl₂, 2H₂O[19]	Lack of catalyst recyclability
8	Platinum(II) terpyridyl acetylide complex/O₂/hν (ref. 22)	Use of costly reagents
9	Au/CeO₂ (ref. 24)	Use of costly reagents
10	I₂/water[25]	Lack of catalyst recyclability
11	2-Nitro-4,5-dichloropyridazin-3(2H)-one[26]	Lack of catalyst recyclability
12	NaNO₂ (ref. 27)	Lack of catalyst recyclability
13	Cellulose supported Cu-nanoparticles	Cost-effective, re-usable heterogeneous catalyst. Works in comparatively milder reaction conditions under microwave heating

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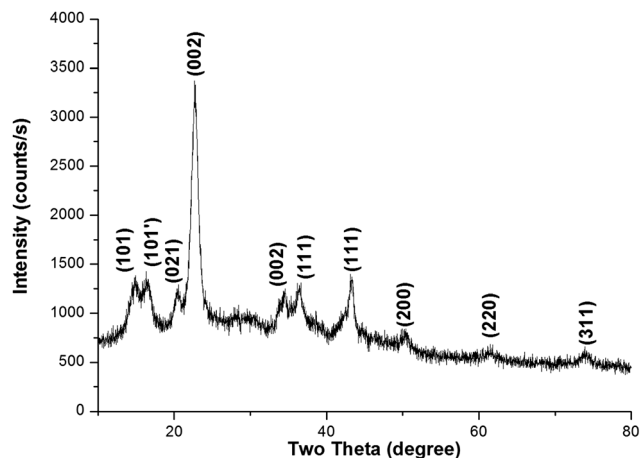
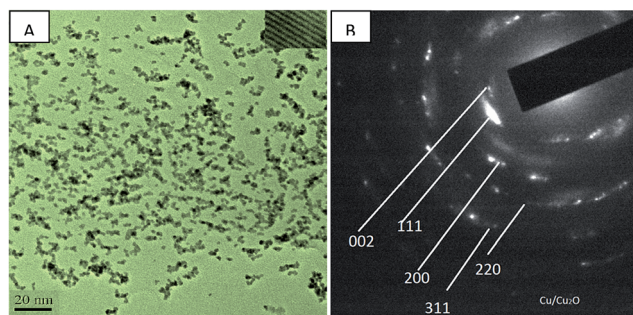Fig. 1 XRD spectra of Cu-nanoparticles on a nanoporous cellulose template.

Fig. 2 (A) TEM and HRTEM (inset) images of the Cu(0)/Cu$_2$O nanoparticles on a cellulose template. (B) Location of selected area electron diffraction (SAED) pattern.

oxidized products, and long reaction time. Moreover, many of the catalysts are homogeneous, and thus cannot be recycled.[25–27] Therefore, the development of an efficient and re-usable heterogeneous catalyst, which can deprotect oximes, imines, and azines in water under neutral conditions can be considered to be highly useful.
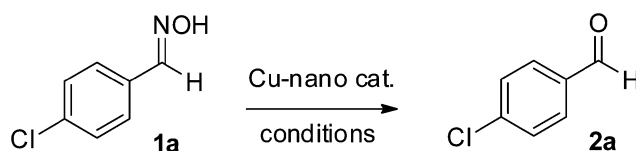
The stabilization of metal nanoparticles using biopolymers, such as cellulose, in place of synthetic polymers is currently attracting increasing importance because of the possible environmental benefits.[28] Cellulose consists of anhydroglucose units joined by an oxygen linkage (β-1-4 glucosidic bond), which forms a molecular chain. As a whole, the structure creates microfibrils with widths of up to 30 nm that are three dimensionally connected to each other.[29] Because of strong electrostatic ion dipole interaction, the metal nanoparticles are stabilized in these microfibrils. Moreover, depending on the different porosities of the microfibril templates, the shape and size of the nanoparticles are varied.[30] Although various properties of cellulose-supported metal nanoparticles have been studied, their potential applications as renewable heterogeneous catalyst have not yet been widely explored. In this context, herein, we report the application of cellulose-supported Cu-nanoparticles as a renewable green catalyst for the efficient deprotection of C=N bonds of oximes, imines and azines to their corresponding carbonyls.

In continuation of our ongoing work on nanomaterials,[31] we were interested in studying the catalytic properties of cellulose supported Cu-nanoparticles. Usually, cellulose-supported Cu-nanoparticles are prepared by reducing Cu(II) on a cellulose surface using sodium borohydride.[32] We have prepared the nanoparticles using hydrazine hydrate/NaOH as a reducing agent in place of NaBH$_4$. It was found that the reduction of Cu(II) acetate on cellulose using either of the two processes provided a stable black colored Cu-cellulose mixture. An initial powder X-ray diffraction study (XRD) showed that in combination with four cellulose peaks at 2θ values of 14.8°, 16.4°, 20.4°, and 22.9°, corresponding to the Bragg's planes (101), (101′), (021), and

and 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-

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	H$_2$O	80 °C	5 min	89

[a] Reactions are carried out using 1 mmol substrate. [b] Yields refer to isolated yield.
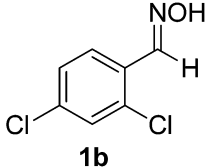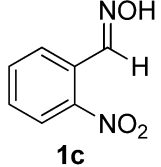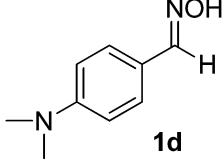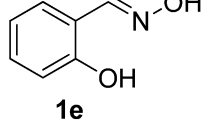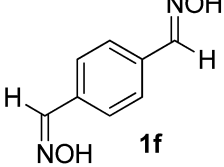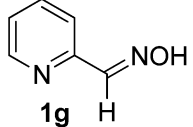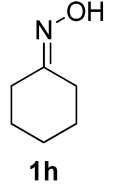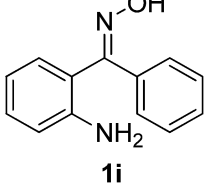
(002), there were four additional peaks at 2θ values of 34.4°, 36.3°, 61.4° and 74.1° corresponding to the (002), (111), (220) and (311) planes, representing Cu_2O, and another two distinguished peaks at 2θ values of 43.2° and 50.4° corresponding to the (111) and (200) planes, representing Cu(0) (Fig. 1). No peaks corresponding to Cu(II) or any other impurity were 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 an average size of 6 nm (Fig. 2). The high resolution TEM identified the reticular lattice planes inside the nanoparticles, indicating their crystalline nature.

To find out the catalytic properties of the prepared Cu-nanoparticles, the deoximation of 4-chlorobenzaldehyde oxime (**1a**) was studied. Refluxing a mixture of **1a** and the Cu-nanocatalyst in acetonitrile provided the corresponding aldehyde **2a**, but the yield was low and the reaction time was also very long (Entry 1, Table 2). Influenced by the reports of a dramatic reaction rate acceleration and yield improvement by microwave irradiation, it was decided to carry out the reaction under microwave irradiation.[33] Therefore, the same reaction was repeated under microwave irradiation in a sealed vial, which provided a reasonably good yield of the product **2a** in a considerably less time (Entry 3, Table 2). The requirement of the metal nanoparticles in the reaction was established by performing two blank reactions, where the 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 a catalytic amount of nanoparticles was sufficient to carry out the reaction, and also that water could effectively be used as solvent. Under the optimized reaction conditions, a mixture of **1a** and a catalytic amount of Cu-nanoparticles 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 smoothly proceeded to produce the corresponding carbonyls. Although the rate of the reactions did not significantly change, the yields somehow varied with the substituents present in the compounds. The electron-donating substituents, such as –OH, –NMe$_2$, and NH$_2$, led to a comparatively lower yield of the products. The catalyst was equally effective for both, aldoximes and ketoximes. All the products were well characterized by the comparison of their physical characteristics (TLC R_f value and melting point) and spectral data (IR and NMR) with those of the authentic samples.
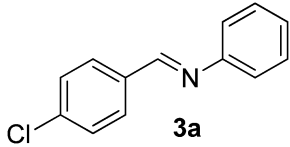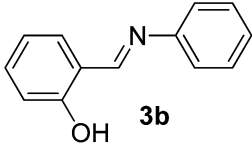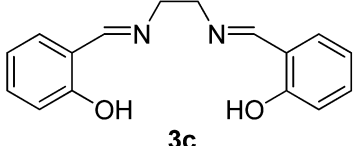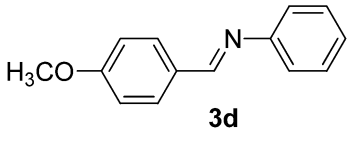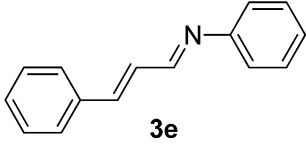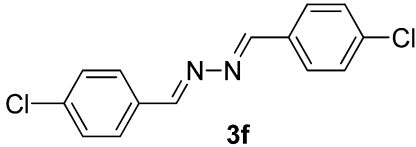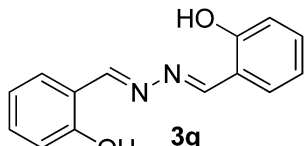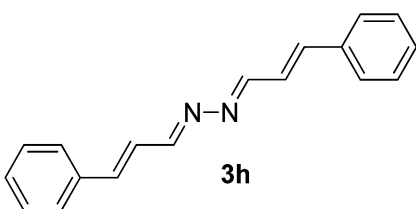
After the successful experiment with oximes, the deprotection of imines and azines were studied. It was observed that the catalyst was also able to efficiently cleave imines and azines to their corresponding amines and carbonyls (Table 4). A number of different imines and azines were deprotected using the standardized reaction condition. In this case, the yield also varied with the nature of the substituents. For all the reactions, the formation of over-oxidized products, such as acid or acid decarboxylated compounds, were not observed. Different sensitive functional groups, such as hydroxyl and alkene, were well tolerated in the reaction condition. All the products were well characterized by co-TLC expression and by comparison of the melting point, IR, and NMR data with the corresponding

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	**1i**	100/8	79

[a] Reaction conditions: mixture of oxime (1 mmol), Cu-nano catalyst (20 mol%), and H_2O (5 mL) was heated in a sealed microwave vial at a given temperature for the stipulated time. [b] Yields refer to the isolated yield of the carbonyls.

Table 4 Deprotection of imines and azines[a]

Entries	Imines and azines	Temperature (°C), time (min)	Yield[b] (%)
1	**3a**	80/5	88
2	**3b**	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

[a] Reaction condition: Mixture of imines/azines (1 mmol), Cu-nanocatalyst (20 mol%), and H_2O (5 mL) was heated in a sealed microwave vial at a given temperature for the stipulated time. [b] Yields refer to the isolated yield of the carbonyls.

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 (Fig. 3).

There are two different mechanisms reported for the Cu-catalyzed deprotection of oximes, imines, and azines.[18,19]

While oxidative deoximation is proposed for Cu(I) promoted reactions,[18] in the case of Cu(II),[19] it is only the co-ordination with nitrogen that 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
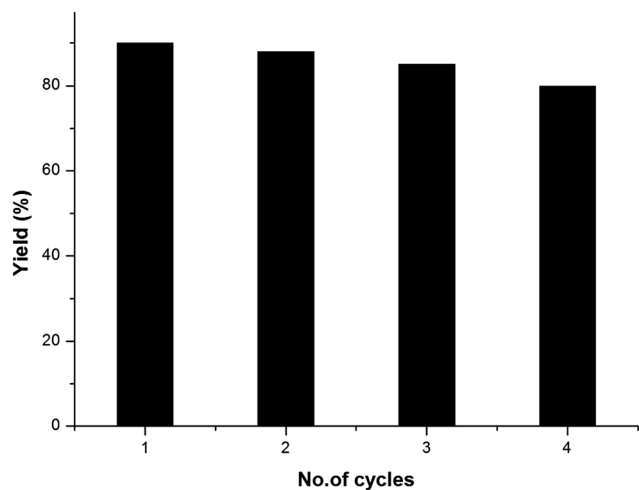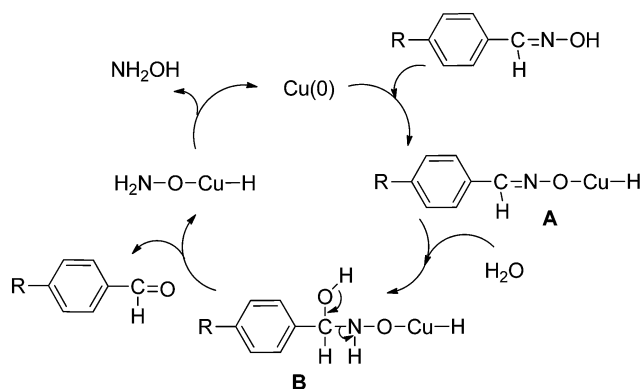
Fig. 3 Study of the catalyst recyclability for the deoximation of *p*-chlorobenzaldehyde oxime (**1a**).

possibility of oxidative deoximation, an experiment was carried out under a strict inert atmosphere. It was observed that the reaction was equally effective under the inert atmosphere as well. In this situation, the co-ordination of Cu(0)/Cu(I) with the nitrogen of C=N is the most possible mechanism for the deprotection of the oximes, imines, and azines. An alternative mechanism may also be possible for oximes only. It starts with the oxidative insertion of Cu(0) into the oximes to produce an intermediate **A** (Scheme 1). Subsequently, the nucleophilic attack of water cleaves the C=N *via* intermediate **B**, thus releasing the carbonyls.

In conclusion, cellulose-supported Cu-nanoparticles were shown to be an effective heterogeneous catalyst for deprotecting oximes, imines, and azines to their corresponding carbonyls and amines. The superiority of the catalytic system over the other existing reactions can be described by few salient features, such as 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, and clean reaction profile. Studies for the application of the catalytic system towards more complex substrates and different reactions are being performed.

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

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