Sustainable Chemistry

CuO Nanoparticles as a Simple and Efficient Green Catalyst for the Aziridine Ring-Opening: Examination of a Broad Range of Nucleophiles

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It has been observed that CuO nanoparticles act as effective and reusable catalyst for the ring-opening reaction of aziridines with a wide range of nucleophiles such as alcohols, thiols, and indoles. The catalytic activity has been tested in large scale reactions. The methodology is applicable in very low catalyst loading. The reaction proceeds under solvent-free conditions. The catalyst has been used for six consecutive cycles with comparable efficiency. The present methodology could be considered as environmentally benign as indicated by the calculation of E-factors which are very low in the range of 0.37–1.31.

Introduction

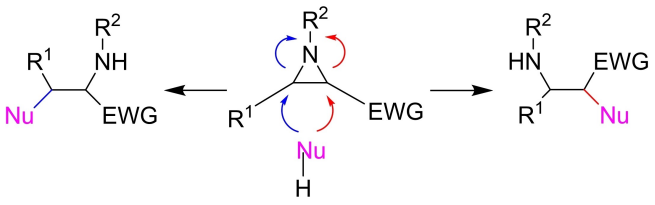
Environmentally benign catalysts are very effective in economical as well as ecological sense.[1] The use of metal nanoparticles (NPs) as catalysts in organic synthesis is increasing day by day. Nanoparticles have a large surface area and consequently are much reactive.[2] These are very stable and can easily be recovered and reused. Recently different metal oxide nanoparticles like zinc, copper, magnesium, iron, titanium have been synthesized. Among these, CuO nanoparticles attract too much attention and has been applied in various organic transformations.[5,6]

Prof. Sheldon, in 1992, used the E-factor which helps to determine the waste produced per Kg of the product.[7] Recently, the practice of green chemistry has gained much attention and chemists are always trying to avoid the harmful solvents in chemical reactions. So, accordingly, the neat reaction or solvent-free reaction is very popular for modern synthetic organic transformations.[8]

In synthetic organic chemistry, synthesis as well as the ring-opening reaction of aziridines are very significant.[9] This small nitrogen heterocycle is a very important synthon to synthesize various biologically active molecules.[10–14] Particularly the ring-opening products are very important in medicinal chemistry as well as synthetically valuable in fundamentally important transformations..[15–18]

Though the ring-opening of aziridine commonly occurred in S_N2-mechanism regio-selectivity is not always predictable. Ring-opening may possible in both S_N1 and S_N2 mechanisms which depends on the N-activation as well as substituents pattern in the aziridines (Scheme 1).[19]

Usually, 1,2-difunctionalized compounds are produced by simple ring-opening of aziridines like diamines, aminols, amino ether, etc. by various nucleophiles using different catalytic systems.[20–27] Yadav and his group reported an oxidative and regioselective ring-opening of aziridine using a catalytic amount of lithium perchlorate[28] and Dess-Martin periodinane (DMP) and silica were used in another work.[29] Das *et al.* used ammonium-12-molybdophosphate as a heterogeneous catalyst[30] and another one is a catalyst-free method[31] for regioselective ring-opening of aziridines. In the presence of visible light using photoredox catalyst like $[Ru(bpy)_3]Cl_2$ has been reported by Xia's group.[32] Regardless of their efficiency and reliability, most of these methods suffer from one or more disadvantages such as the use of expensive reagents and catalysts, reusability of the catalysts, long reaction times,



Scheme 1. Regioselectivity of carbon-nitrogen bond cleavages in nucleophilic aziridine ring-opening.

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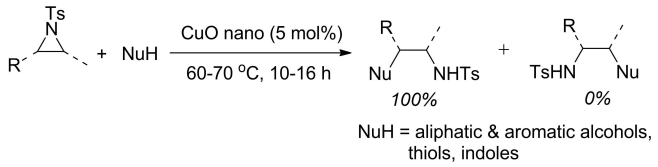
requirement of an inert atmosphere and harsh reaction conditions. We are also engaged in aziridine chemistry[33,34] as well as nanocatalysis.[35] As a combined effort herein, we report an efficient method for ring-opening of aziridines using copper oxide nanoparticles as a reusable catalyst by various nucleophiles (Scheme 2). Our reported method is mild enough and carried out in neat reaction conditions using various types of nucleophiles like alcohols, thiols, indole, etc.

Results and Discussion

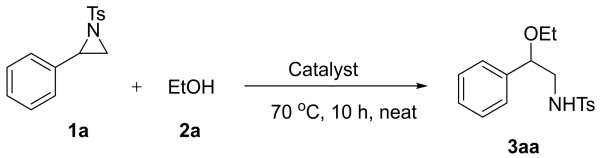
During our initial study, phenyl *N*-tosylaziridine (**1 a**) and ethanol (**2 a**) as the nucleophile were taken as model substrates using 5 mol% of CuO nanoparticles as the catalyst and the reaction was carried out at 70 °C for 10 h in absence of any other solvents (Table 1, entry 1). The desired product *N*-(2-ethoxy-2-phenylethyl)-4-methylbenzenesulfonamide (**3 aa**) was obtained in 80% yield. After this initial observation we optimized the reaction which is summarized in Table 1. We have tested different metal nanocatalysts e.g. In_2O_3, NiO, ZnO (Table 1, entries 2–4), but only 5 mol% of CuO nano (Table 1, entry 1) showed best catalytic activity. Simple CuO powder (Table 1, entry 5) and other copper salts (such as $Cu(OAc)_2$, CuBr, $CuCl_2$, CuI, Cu_2O, $Cu(OTf)_2$) were not so effective for this reaction under similar conditions (Table 1, entries 6–11). By increasing the amount of catalyst from 5 to 10 mol% no improvement of the reaction was observed. Very less amount of desired product was obtained in the absence of any catalyst (Table 1, entries 14). We have not tested the reaction in the presence of solvent as we got satisfactory results under neat conditions. So, the reaction of phenyl *N*-tosylaziridine (**1 a**, 1 mmol) and ethanol (**2 a**, 2 mmol) using 5 mol% of CuO nano at 70 °C for 10 h under neat conditions is the optimal reaction conditions (Table 1, entry 1).

After optimization, we examined different aziridines reacting with various nucleophiles such as alcohols, thiols, indoles to test the usefulness of our methodology which are shown in Table 2. Simple aryl *N*-tosylaziridine (**1 a**) reacted with methanol (**2 b**) and *n*-propanol (**2 c**) very smoothly to give the corresponding **3 ab** and **3 ac** in 75% and 84% yield respectively. Simple aryl *N*-tosylaziridine (**1 a**) reacted with a number of aliphatic (**2 d**–**2 i**) and aromatic alcohols (**2 j**–**2 o**) to give the corresponding products (**3 ad**–**3 ao**) with satisfactory yields. Allylic, as well as propargylic alcohols, reacted with **1 a** without any difficulty (**3 ae**--**3 ag**). Aromatic alcohols containing electron-donating substituents (-Me, –OMe) showed also good efficiency (**3 aj**- **3 al**). Similarly, halogen-substituted aromatic alcohols such as -I and -Br (**3 am**–**3 ao**) smoothly reacted with *N*-tosylaziridine (**1 a**). Next, we turned our attention to use other nucleophiles such as thiols and indoles. Phenyl *N*-tosylaziridine (**1 a**) reacted smoothly with aliphatic (**2 p**) and aromatic thiols (**2 q**–**2 u**) and afforded the products (**3 ap**–**3 au**) in good yields. The thiophenols with electron-donating substituents like –Me, –OMe (**3 aq** & **3 ar**) and electron-withdrawing groups like –Cl, –F reacted also to afford the desired ring-opening products (**3 as** & **3 at**). Simple aryl *N*-tosylaziridine (**1 a**) also reacts with indole (**2 v**) to give the corresponding **3 av** in 76% yield. Other substrates of aziridines like 2-(4-chlorophenyl)-1-tosylaziridine



Scheme 2. CuO nano-catalyzed ring-opening of aziridines.

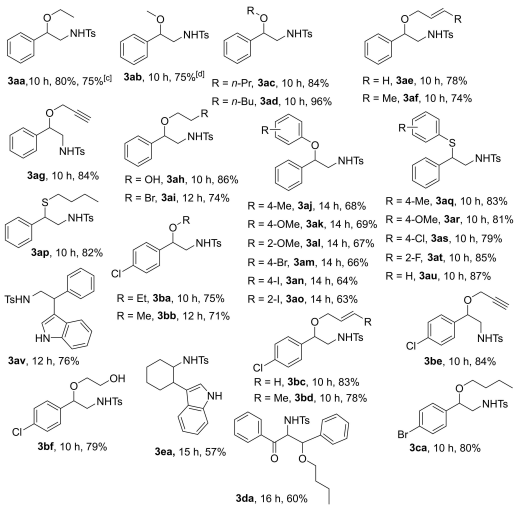
Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst (mol%)	Yield[b] (%)
1	CuO nano (5)	80
2	In_2O_3 nano (5)	35
3	NiO nano (5)	44
4	ZnO nano (5)	48
5	CuO (5)	65
6	$Cu(OAc)_2$ (5)	38
7	CuBr (5)	40
8	$CuCl_2$ (5)	32
9	CuI (5)	51
10	Cu_2O (5)	70
11	$Cu(OTf)_2$ (5)	68
12	CuO nano (10)	80
13	CuO nano (3)	62
14	–	30

[a] Reaction conditions: **1 a** (1 mmol), **2 a** (2 mmol), temp: 70 °C, neat conditions, 10 h. [b] Isolated yields.

Table 2. Ring-opening of aziridines with various nucleophiles.[a,b]



[a] Reaction conditions: aziridines **1** (1 mmol), nucleophiles **2** (2 mmol for aliphatic alcohols, 1 mmol for aromatic alcohols as well as thiols and indole), CuO nano (5 mol%) at 70 °C. [b] All are isolated yields. [c] Phenyl *N*-tosylaziridine (**1 a**, 10 mmol) and EtOH (**2 a**, 20 mmol) in the presence of CuO nano (5 mol%) at 70 °C for 10 h. [d] Reaction was carried out at 60 °C.

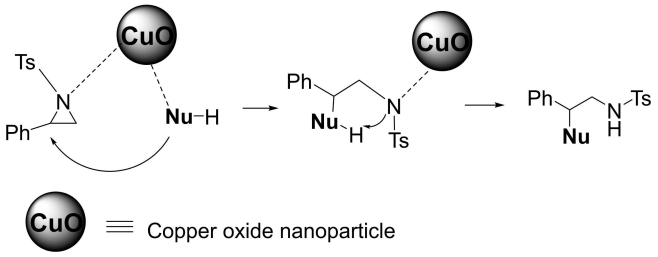
(**1 b**) and 2-(4-bromophenyl)-1-tosylaziridine (**1 c**) gave the same type of nucleophilic ring-opening reactions. 2-(4-Chlorophenyl)-1-tosylaziridine (**1 b**) reacted with a number of aliphatic alcohols to give corresponding benzenesulfonamides **(3 ba**–**3 bf)** with good yields. 2-(4-bromophenyl)-1-tosylaziridine (**1 c**) also reacted with butan-1-ol (**2 d**) to give the desired product **3 ca** in 80% yield. Aziridines with carbonyl group were also examined and it remained unreacted in the presence of *n*-BuOH (**3 da**). It is worthy to mention that aliphatic aziridine is equally reacted with indole and afforded the desired product (**3 ea**) in moderate yield.

Spectral and analytical data have been recorded for all the compounds and compared for the reported ones. We observed that the reactions afforded the products resulting from the benzylic attack. No decomposition, polymerization or by-products has been observed for all reactions which demand the mildness of our protocol. The applicability of this methodology is demonstrated for the synthesis on the gram scale. When the model reaction was performed on gram scale the corresponding product (**3 aa**) was obtained in 75% yield (2.39 g). This observation demonstrates the potential applications of the present method for large-scale synthesis of ring-opening product *N*-(2-ethoxy-2-phenylethyl)-4-methylbenzenesulfonamide (**3 aa**).

Table 3. Recycling of CuO nano for synthesizing **3 aa**.[a]

No. of cycle	Yields (%)[b]	Catalyst recovery (%)
1	80	95
2	78	91
3	75	87
4	72	85
5	69	82

[a] Carried out with 1 mmol of **1 a** and 2 mmol of **2 a** in presence of CuO nano (10 mol%) at 70 °C for 10 h. [b] Isolated yields.



Scheme 3. Proposed reaction mechanism.

We have tested the reusability of the catalyst. After completion of the reaction, ethyl acetate (10 mL) was added in the reaction mixture and CuO nanoparticles were recovered from the reaction mixture by filtration through the Teflon membrane (PTFE, 0.2 mm pore size). Ethanol was used to wash the recovered CuO nanoparticles and reused them after proper drying. The efficiency of the catalyst has been tested to synthesize the compound **3 aa** for five times. As shown in Table 3, the efficiency is comparable after five times. The morphological study of the HRTEM of the fresh catalyst and the recovered catalyst after fifth cycles (Figure 1) has been compared which showed no agglomeration throughout the recycling procedure.

We have calculated the E-factors[7] for this ring-opening reaction of aziridines catalyzed by CuO nano (Supporting Information, Table 1) which shows the green nature of this approach considering the principles of the atom economy.

Based on literature and our previous observations[33] we proposed a probable mechanism (Scheme 3) where the aziridine is activated by CuO nano through the co-ordination with nitrogen atom of aziridine group. It is well documented that highly dispersed CuO particles possess acidic properties, in

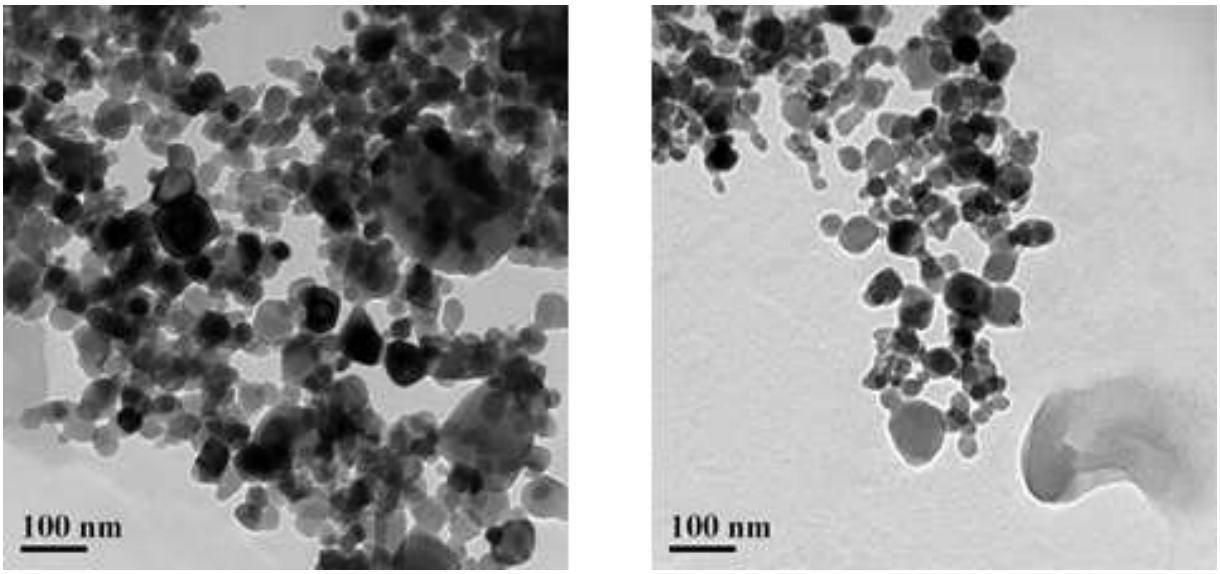
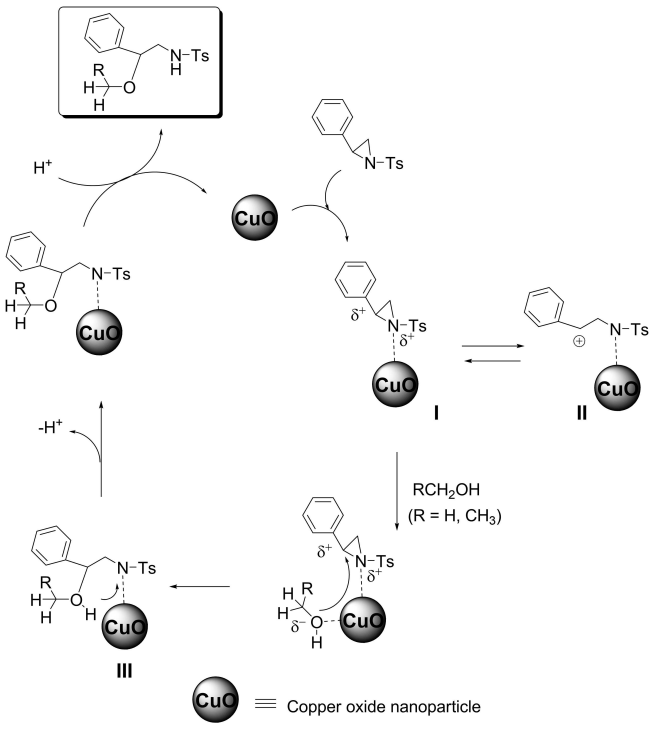


Figure 1. HRTEM images of fresh CuO NPs (left) and CuO NPs (right) after the fifth cycle.

particular, they can catalyze the ring-opening of phenyl-substituted epoxides under the action of O- and N-nucleophiles. This acidity (Lewis type of Brønsted type) is associated with a high content of broken metal-oxygen bonds in highly dispersed metal-oxide particles. These are obtained when the surface of bigger metal oxide crystal as an ideal lattice plane becomes exposed by cutting/breaking this bigger crystal to the ultra-smaller ones (or NPs) resulting in exposed metal centers which are coordinatively unsaturated and, thus, highly reactive, *i.e.* acidic. Thus, the CuO NPs might both to catalyze the aziridine ring towards the nucleophilic attack and to stabilize the transition state of the reaction during the attack of different nucleophiles in an S_N2 fashion to provide the ring-opening final products.

We have shown a reaction pathway for a specific nucleophile such as methanol (Scheme 4). In the first step, the azaphilic activation of aziridine by CuO NPs catalyst reversibly produces an activated complex **I**. The intermediacy of the open-chained carbocation **II** is also possible. In the case of hard small nucleophiles, such as MeOH, they react with complex **II** *via* the S_N2-type mechanism with high regioselectivity at the most positively charged benzylic carbon of **I** to produce new intermediate **III**. Again, the intermediacy of a zwitterionic specie **III** could not be disregarded and in this case, the reaction would provide intermediate **III** by S_N1-type mechanism.

The similarity of the results observed for the methanol as nucleophile could be attributed to their better adsorption on the surface of CuO catalysts, and methoxy- species are better stabilized and, thus, can be easily delivered to the most positively charged reaction site of the aziridine. This phenomenon is widely studied on the metallic copper surface.



Scheme 4. Proposed reaction pathway for methanol and ethanol as nucleophile.

Conclusions

In conclusion, the CuO nano has been found to be a highly efficient catalyst for the nucleophilic ring-opening of aziridines. The advantages of this transformation include a broad range of nucleophiles, good yields, neat reaction conditions, low catalyst loading and reusability of the catalyst. Verities of alcohol and thiols have been used as nucleophiles for this transformation. Indoles were also examined as a soft nucleophile for this ring-opening reaction. The CuO nanocatalyst can be easily recovered and reused with comparable activity. Calculated E-factors of this copper oxide-nano particles-catalyzed aziridine ring-opening reaction proved the lowest generation of waste. The extension of this methodology for the gram-scale synthesis demonstrates the potential for industrial applications.

Supporting Information Summary

The Supporting Information for this article contains the Experimental Section explaining all the experimental details along with general procedure, analytical and spectral data of all the synthesized compounds, E-factors and scanned copies of their respective ^{1}H-NMR and ^{13}C-NMR spectra.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: alcohols · aziridine ring-opening · nanoparticles · sustainable chemistry · synthetic methods

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