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A green and facile ultrasound-promoted synthesis of thioamide derivatives catalyzed by Cu(I)@chitosan as a new bio-polymeric nano catalyst in aqueous media

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Abstract: The three-component Willgerodt–Kindler reaction with was efficiently catalyzed by the Cu(I)@chitosan as a heterogeneous nano-bio catalyst to afford the corresponding thioamides in high to quantitative yields in short reaction times and mild conditions. The Cu(I)@chitosan can be recovered at least 4 times without significant loss of its catalytic activity. The reaction was carried out in the aqueous media.

Keywords: *Bio polymeric nano catalyst, Willgerodt-Kinler reaction, Thioamide, Ultrasonic irradiation.*

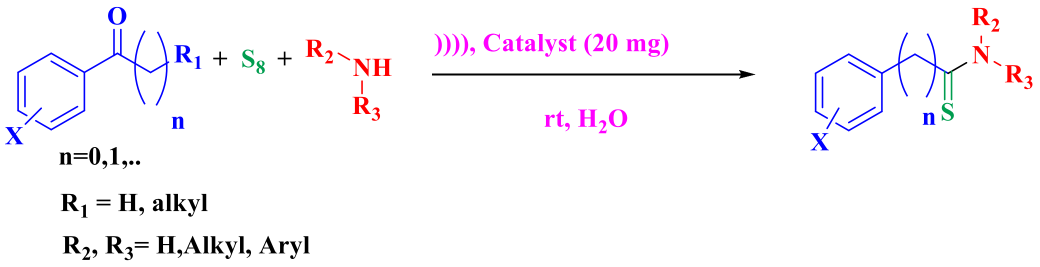
Introduction

Thioamide are great importance in medicinal chemistry due to their biological activity. For example, against bacterial infection, anti-fungicides, herbicides and anti-ulcerative agents. Thioamide intermediates are versatile in synthesis of pharmaceutical ingredients, such as Diclofenac, Fenclofenac, Ibufenac, Naproxene, in peptide chemistry [1] and as a building blocks for the synthesis of five- and six-membered heterocyclic scaffolds.[2] Furthermore, the thioamide derivatives can be readily converted to the corresponding carboxylic acids or thioesters. Therefore, developing of more efficient methods working under mild condition is in high demand.[3] Thioamides are traditionally prepared by thionation of the corresponding amides using phosphorus pentasulfide or the Lawesson's reagent.[4] Surprisingly, the Willgerodt–Kindler reaction for thioamide synthesis has received very little attention (especially in recent years). Today, the Willgerodt–Kindler reaction can be classified as a one-pot, three-component process for the synthesis of synthetically useful (thio) amides.

Typically, it is accomplished using a ketone or aldehyde, elemental sulfur and an amine (or ammonia) at elevated temperatures. Due to the wide range of commercially available derivatives of reaction components, a diverse library of corresponding thioamides containing products from this reaction can be envisaged. Classical Willgerodt-Kindler reaction, which has limited applications, because of high temperatures (120^{o}C)[5] long reflux times around 6-8 hours[6] and low to moderate yields.[3] Many modified conditions have been used in synthesis of thioamide intermediates such as using microwave irradiations[7, 8], ionic liquids [9] hazardous solvents (DMF or DMSO)[10-12] and anion-exchange resin, [13]. Most of these protocols suffer from long reaction times, high temperature, using volatile solvents, harsh reaction conditions, use of expensive reagents and difficulty of reusability the catalysts.

Chitosan as a linear polyamine is the most important derivative of chitine, the second most abundant natural polymer in the world after celloluse. The presence of free NH_2 groups in chitosan and its insolubility in most organic compounds and pure water for using as a heterogeneous catalysis[14]. Chitosan could be chelated to several metallic ions such as Cu, Pd, Au, Cr and Cd [15] for waste water treatment was one of the first applications for chitosan. The interaction of metals with chitosan are complex, probably simultaneously dominated by adsorption and chelation.

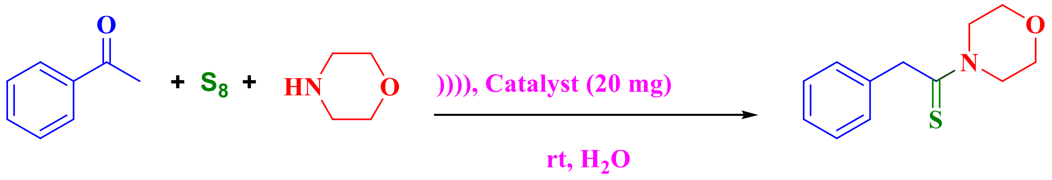
In continuation of our interest to use biopolymers for organic transformations, Copper immobilized on chitosan was used as an efficient heterogeneous nano-biocomposite catalyst for Willgerodt–Kindler reaction of ketones or aldehydes, elemental sulfur and secondary amines. This catalyst can be play a major role in thioamide bond formation. Easy preparation and separation, mild acidity and basicity, stability and reusability motivated us to explore its potential to catalyze reaction (Scheme 1).



Scheme 1: Synthesis of thioamide derivatives using Cu(I)@chitosan as a catalyst.

Experimental

A mixture of acetophenone(1 mmol), Sulfur(2 mmol) and morpholine(1.2 mmol) was sonicated in aqueous media at ambient temperature in the present of catalyst (20 mg) for 2.30 h to obtained 86% of 1-morpholino-2-phenylethanethione (Scheme 2). After completion of the reaction as indicated by TLC, the reaction mixture was diluted with cold water. The catalyst was separated easily from the precipitated product, the filtered solid was then recrystallized in ethanol.



At first, acetophenone, morpholine and sulfur were selected as model substrates to optimize the reaction conditions and sonicated (P=150 W). As shown in table 1, the best loading catalyst was 20 mg in aqueous media at ambient temperature.

Table 1: Selected results from an optimization of the reaction conditions.

Entry	Catalyst Loading (mg)	Solvent	Conditions	Time(h)	Temperature(^{o}C)	Yield (%)
1	---	Water	U.S	12	rt	0
2	**20**	**Water**	**U.S**	**2.30**	**rt**	**86**
3	20	EtOH	U.S	2.50	rt	75
4	20	CH_3CN	U.S	3.40	rt	53
5	20	CH_2Cl_2	U.S	4.30	rt	27
6	25	Water	U.S	2.30	rt	87
7	15	Water	U.S	2.30	Rt	80

Synthesis of thiomorpholide from acetophenone, morpholine and sulfur under ultrasound irradiation. The optimized conditions was 20 mg of nano polymeric copper immobilized on chitosan at room temperature under ultrasound irradiation in water (table 2).

Table 2: Synthesis of thioamide derivatives by using nano catalyst of Cu(I)@chitosan.

Entry	Ketone	Amine	Time (h)	Yield (%)
1	Acetophenone	Morpholine	2.30	86

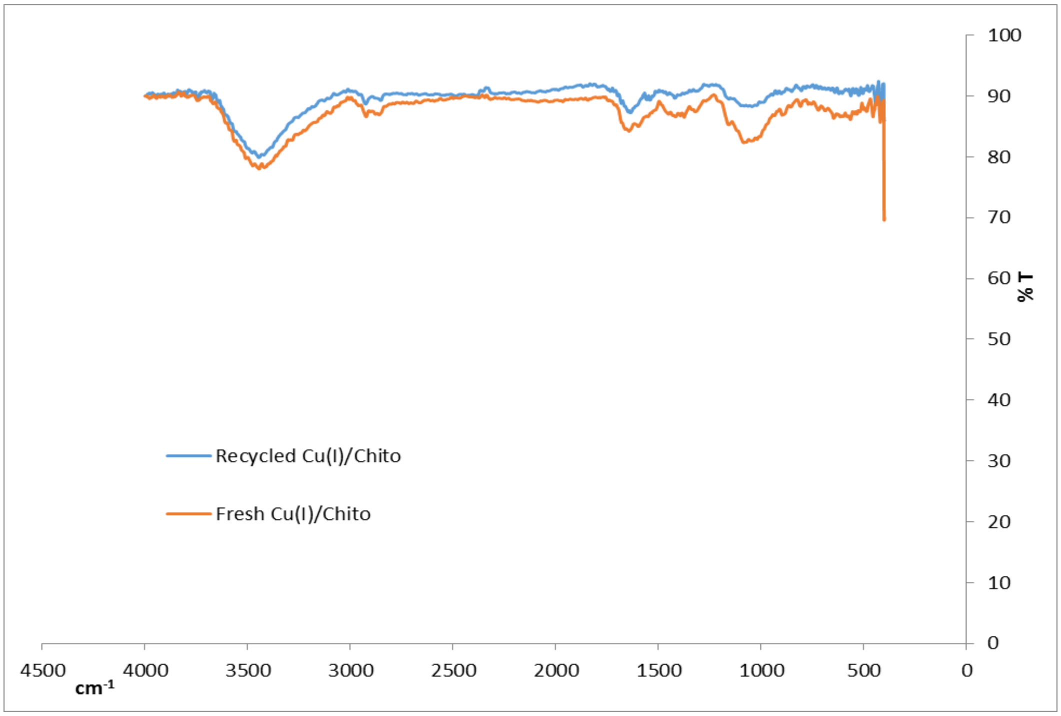
2	4-chloro acetophenone	Morpholine	2.15	75
3	4-nitro acetophenone	Morpholine	1.30	87
4	4-methoxy benzaldehyde	Morpholine	2.30	70

Results and discussion

A ratio of 1:1.2:2 mixture of acetophenone, morpholine and sulfur was sonicated. The best results were obtained in the present of water as a green solvent. Elecrton-withdrawing substituents were obtained higher yield in shorter reaction times than electron-releasing substituents. For example, group of nitro in *para* has the least steric hindrance than *ortho* or *matha* positions. Electron-donor groups, methyl- or methoxy acetophenone gave the product in good results, (4-methoxy acetophenone= 70%, entry 4). In addition, the reusability of this heterogeneous nano catalyst is one of its important point. By washing with acetone and water, then drying it at 50^{o}C in oven it can be reused several times. The reusability of this catalyst was shown by FT-IR spectra of fresh with recycled catalyst in table 3. After using five times of Cu(I)@Chitosan in this reaction, there was no significant loss of its catalytic activity.(Scheme 2)

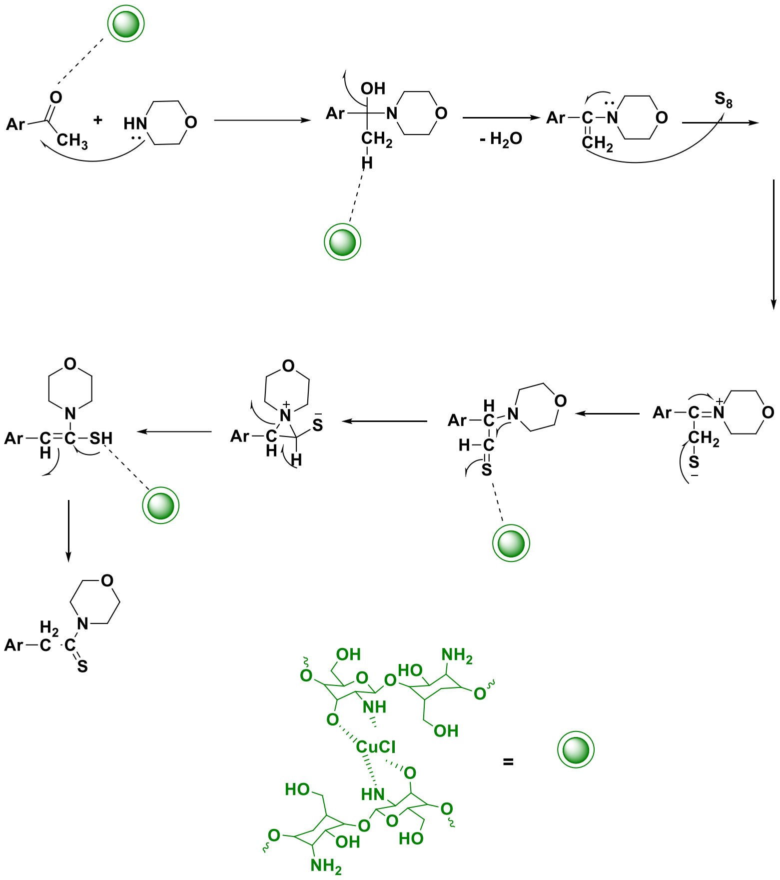
Table 3: Reusability of the nano catalyst on the model reaction

Run	**Fresh**	**1**	**2**	**3**	**4**	**5**
Yield (%)	86	86	84	80	77	71



Scheme 2: FT-IR of fresh catalyst and recycled catalyst after five times using in reaction.

In recent years heterogeneous catalysts have attracted a great attention due to efficiency, and for economic and environmental reasons. In the green chemistry context, replacement of homogeneous catalysts with heterogeneous ones for the productions of fine chemicals in industrial processes appears as expansive research area**.** Nano particle of copper on chitosan acts as a heterogeneous catalyst in Willgerodt-Kindler reaction**.** We have suggested a mechanism, at first, carbonyl group was activayed by catalyst then, morpholine was added to the carbonyl group. Chitosan helps to remove water to form immine intermediate. Polysolfide acts as an electrophile because of empty d orbital. Next step, thione group was activated by catalyst to for aziridine intermediate, after that by omitting hydrogen sulfide the thioamide group was formed (Scheme 3).



Scheme 3: The mechanism of Willgerodt-Kindler reaction by Cu(I)@chitosan catalyst.

Conclusions

In conclusion, we have reported sonochemical method and facile non-thermal Willgerodt-Kindler reaction. This catalyst can be played a major role in thioamide bond formation. Easy preparation and separation, mild acidity and basicity, stability and reusability motivated us to explore its potential to catalyze reaction.

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