One Pot Copper catalyzed Conversion of Oxime to Thioamide

A Dissertation Submitted in partial fulfilment

For the degree of

MASTER OF SCIENCE IN CHEMISTRY

Under The Academic Autonomy

Submitted by:

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Acknowledgement

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Place: Rourkela Sincerely,

Date: 6th May, 2014

Paulami Bose

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DEPARTMENT OF CHEMISTRY
NATIONAL INSTITUTE OF TECHNOLOGY
ROUKELA

CERTIFICATE

This is to certify that the dissertation entitled "**One Pot Copper Catalyzed Conversion of Oximes to Thioamides"** being submitted by **Ms. Paulami Bose** for the award of Master of Science in Chemistry. This report includes the work done during the period of August 2013-April 2014 in the Department of Chemistry, National Institute of Technology, Rourkela under my supervision. This work has not been previously submitted for any degree in this/ any other institute.

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ABSTRACT

Copper-catalyzed one-pot conversion of aldoximes to thioamides is described in this report. The protocol involving is simple, cheap and compatible with wide range to functional group attached to the starting material.

INTRODUCTION

Thioamides are important structural motifs found in many biologically active molecules (Figure 1).[1] These are also important precursors in numerous organic transformations leading to various fine chemicals, heterocycles etc. [2] From the biochemistry and medicinal point of view, thioamides such as 6-mercapto-purine show antitumor activity [3] and even act as anti-thyroid drugs which are used to control thyrotoxicosis. Peptide modifications are done by incorporating thioamides into peptides as isosters for the amide bond. Such modified peptides, analogous to the native peptide, can reveal the structure-activity relationship (SAR). Analogues of peptides are prevalently used as drugs with an improved oral bioavailability. Thioamides inhibit the activity of enzyme thyroid peroxidase in the thyroid, by reducing the synthesis of triiodothyronine (T3) and thyroxine (T4), thereby blocking the uptake of iodotyrosines from the colloid. They also inhibit the iodine release from peripheral hormone.

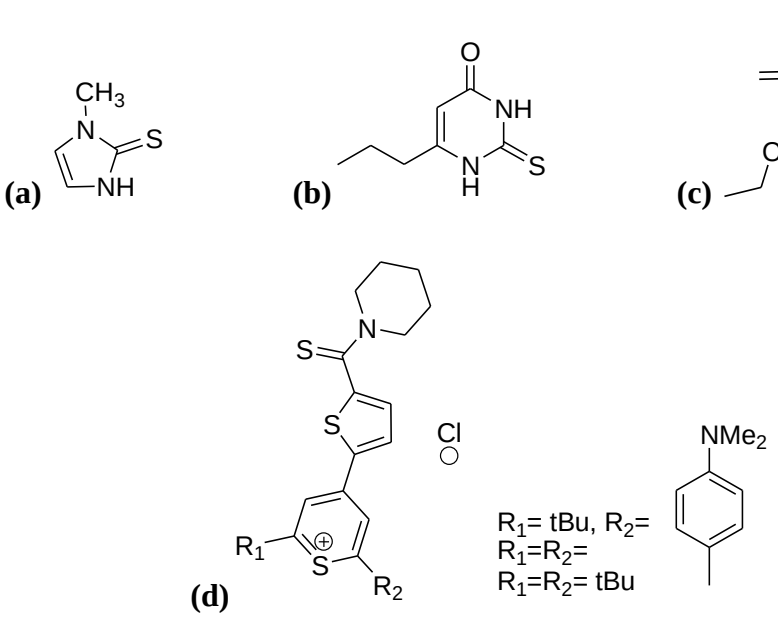
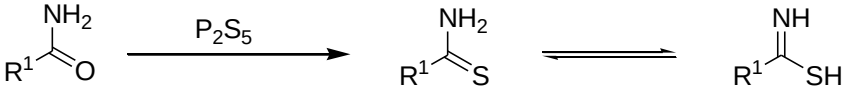


Figure 1. Examples of biologically active thioamide derivative: (a) Methamozole, (b) Polythiouracil, (c) Carbimazole, and (d) Structures of Chalcogenopyrylium Compounds.

In view to the wide use of thioamides for various applications, development of facile and environmentally friendly synthetic methods towards their synthesis is an active area of research. Reaction of amides with thionating agents e.g. P_2S_5 may a general procedure to access thioamides (Scheme 1). [4]

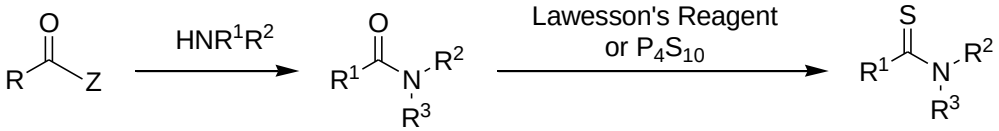
Scheme 1



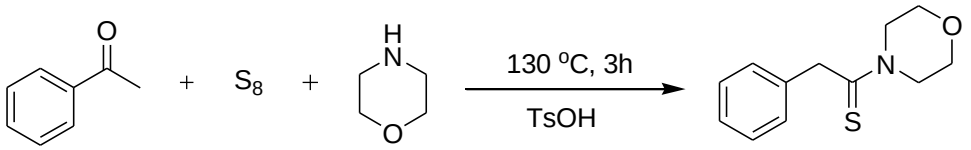
Indeed, some classical methods to achieve thioamides have been developed. For instance, classical methods for the preparation of thioamides usually involve the condensation of carboxyl derivatives and amines to produce amides; which subsequently undergoes thionation with the aid of thionating agents such as P_4S_{10}, Lawesson's reagent, etc., [5] to produce thioamides (Scheme 2). Recently some other useful methods have been developed to achieve thioamides from different precursors. For instance, many reports have been disclosed for the generation of thioamides based on Willgerodt–Kindler method (Scheme 2b). [6] This reaction involves the use of alkyl aryl ketones or aldehydes, elemental sulfur, and amines, with morpholine being the most commonly used amine. Here when the substrate is ketone, the carbonyl group is reduced to a methylene group and the terminal methyl group is oxidized to a thiocarbonyl group. The major limitations of this method are the requirement of long reaction time and lower product yield. Recently, Nguyen and co-workers developed a reaction involving elemental sulfur and two different aliphatic primary amines for the synthesis of thioamides (Scheme 2c). [7] They carried out the reaction of alkynes and amines with elemental sulfur in the presence of pyridines at 60-100 °C to yield thioamides. Jiang and his co-workers (scheme 2d) reported the synthesis of thioamides from the condensation of alkynyl halides, amines and $Na_2S{\cdot}9H_2O$ in DMF at 110 °C. [8]

Scheme 2. Synthetic Approach to Thioamides

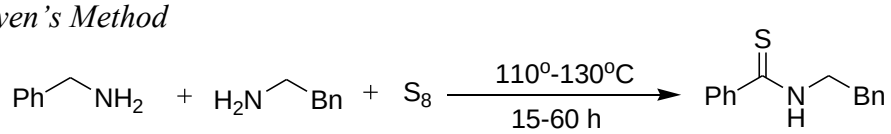
2a. *Classical Methods*



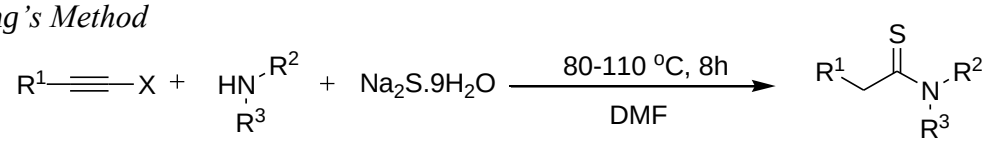
2b. *Willgerodt–Kindler Method*



2c. *Nguyen's Method*

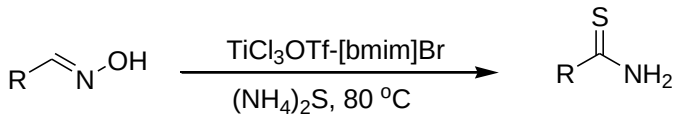


2d. *Jiang's Method*



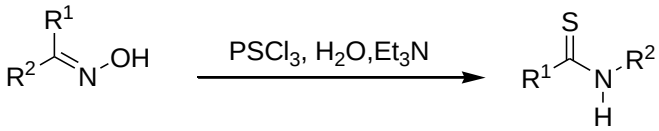
There are some other methods including the direct conversion of oxime to thioamide have also been reported, which include Beckmann rearrangement [9] is the key reaction. The Beckmann rearrangement (i.e. acid catalysed reaction of ketoximes) is one of the direct methods to generate *N*-substituted amides from oximes. Recently, few publications have already reported on the generation of thioamides where oximes are used as a precursor. For instance, Noei and Khosropour used $TiCl_3OTf$ for the chemoselective one-pot transformation of aryl aldoximes to their corresponding thioamides in the presence of phase transfer catalyst such as 1-butyl-3-methylimidazolium bromide ([bmim]Br) (Scheme 3). [10]

Scheme 3



Pathak and his co-workers used $PSCl_3$ reagent in different solvents with varied polarity by heating at 70-90 °C to yield N-Substituted thioamides from ketoximes to induce Beckmann rearrangement (Scheme 4). [11] They have claimed that their thionating agent $PSCl_3$ can not only activate the oxime for Beckmann rearrangement but also reacts with the nitrilium ion formed from the activated oxime and subsequently produce thioamide. The use of this reagent involves serious environmental and operational issues as it is fuming, corrosive, pungent smelling, and moisture sensitive.

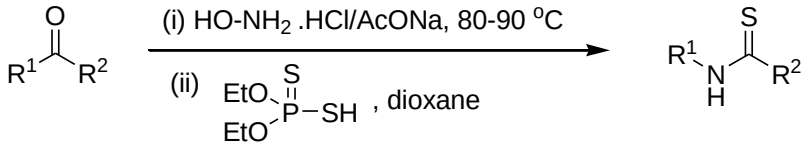
Scheme 4



Yadav and his co-workers have developed a method for a one-pot conversion of aldehydes and ketones into thioamides where the protocol involves first generation of aldoxime and

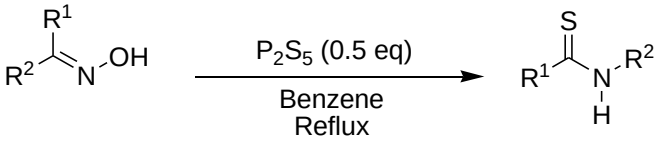
ketoxime at 80-90 °C followed by deoxygenative thioamidation of oximes in dioxane with diethoxy dithiophosphoric acid which acts as an acid as well a source of sulfur (Scheme 5).[12]

Scheme 5



Li and his co-workers had developed a P_2S_5-mediated synthesis of secondary thioamides from ketoximes via Beckmann rearrangement in one step in absence of an extra dehydrating and thionating agent (Scheme 6). [13]

Scheme 6

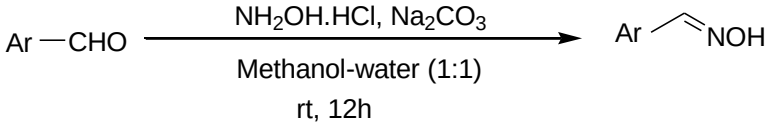


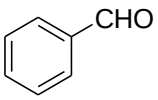
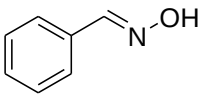
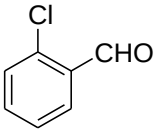
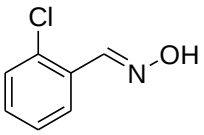
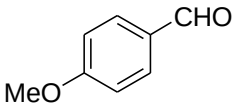
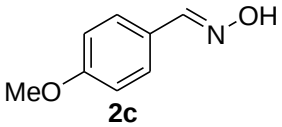
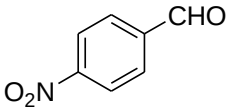
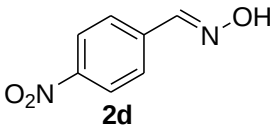
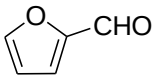
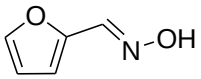
Beckmann rearrangement as already mentioned deals with the conversion of oximes to its corresponding amide but the main disadvantage of the reaction is the requirement of high reaction temperatures and the use of large amounts of strong Brønsted acids and dehydrating media followed by production of large amounts of byproducts. [14] It has been observed that when aldoximes undergoing acid catalysed Beckmann rearrangement leads to nitriles, [15] whereas in the presence of transition-metal catalysts, it leads to primary amides.[16] The transition metal-catalyzed reactions is assumed to proceed through a dehydration/re hydration step via the formation of a discrete nitrile intermediate.[17,18] Eventually, a number of important transition metal (i.e. Rh,[19] Ru,[20] Ir,[21] Pd,[22] and Au/Ag[23]) catalysts were successfully tried for the generation of primary amides from aldoximes. The copper catalysts are cheap, effective at lower catalyst loading and require milder reaction condition, thus making it an attractive choice. Recently, Panda and his co-workers have reported that aldoxime on reaction with aryl halide in the presence of copper catalyst generates *N*-aryl amides in excellent yield. [24] As mentioned above that an oxime can be useful precursor for preparation of its amide so it can be presumed that in the presence of a thionating agent it can subsequently converted into its corresponding thioamide. In line to this concept, here we report the direct conversion of aldoximes to corresponding thioamides in presence of simple copper catalyst.

RESULTS AND DISCUSSION

We started our study using the benzaldoxime as the initial starting material which was synthesized following the traditional method of condensation of benzaldehyde with hydroxylamine hydrochloride in methanol-water (1:1) giving absolutely pure aldoxime in excellent yield. Several other aldoximes were also prepared following the reported method from the corresponding aldehydes.

Table 1. Synthesis of Aldoxime

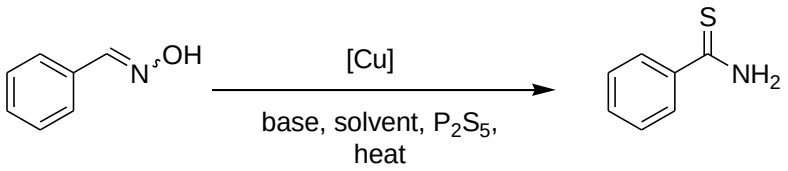


Entry	Aldehyde	Aldoxime	Yield [%]
1	 **1a**	 **2a**	99
2	 **1b**	 **2b**	95
3	 **1c**	 **2c**	94
4	 **1d**	 **2d**	96
5	 **1e**	 **2e**	99

Having aldoxime in our hand we tried to transform into its thioamides. Upon heating the aldoxime **1a** in the presence of $CuSO_4.5H_2O$, K_2CO_3 and P_2S_5 in *o*-xylene, in line with the previous report from our Laboratory, on the copper-catalysed regioselective synthesis of *N*-

Aryl Amides from aldoximes and aryl halides, the reaction gave very poor yield of thioamide along with pungent order of sulphur with considerable charring. The charring may be due to the polymerization of P_2S_5 in the reaction medium thereby creating difficulty in phase separation during workup. We tried to optimize the reaction conditions by identifying the best catalyst, ligand, base, solvent, and reaction temperature. When K_2CO_3 was replaced by Et_3N better yield of thioamide was resulted (80% yield; Table 2, entry 4). Likewise, different copper catalysts were screened (Table 2, entries 3, 4, 5), and CuI (10 mol-%) in the presence Et_3N (2.5 equiv.) afforded the optimum yield of **3a**. Other catalysts such as $CuSO_4.5H_2O$ and CuO were less effective. Even the solvent selection played an important role. Optimized yield was obtained in DMF (Table 2, entry 4). When the reaction was carried out in water no reaction takes place. Upon performing the reaction at 140 °C in DMF, the optimum yield of **3a** was obtained. However, lowering the temperature to 120 °C in DMF did not furnish **3a** even on heating for 48 h. Following the optimum reaction condition some other thioamides were prepared as shown in Table 3.

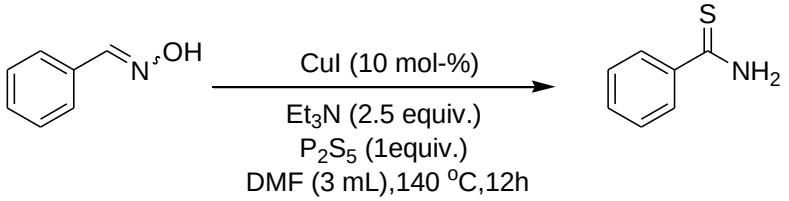
Table 2. Optimization of the Reaction Condition[a]

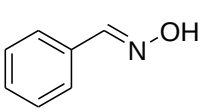
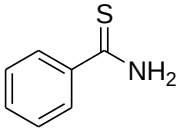
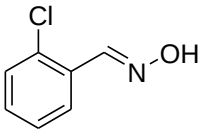
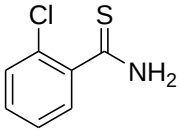
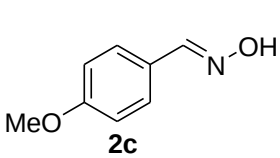
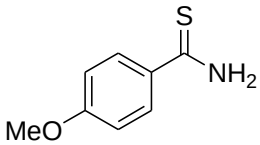
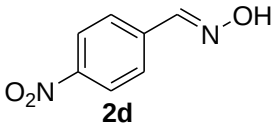
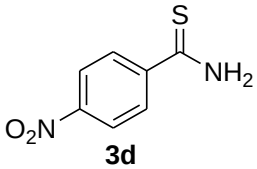
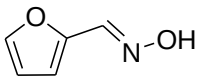
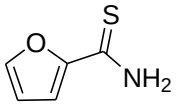
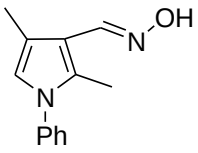
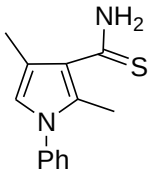


Entry	Catalyst	Base	Solvent	Yield[b] [%]
1	$CuSO_4.5H_2O$	K_2CO_3	*o*-xylene	0
2	$CuSO_4.5H_2O$	K_2CO_3	Water	n.r.
3	$CuSO_4.5H_2O$	Et_3N	DMF	10
4	CuI	Et_3N	DMF	80
5	CuO	Et_3N	DMF	0

[a] Reaction conditions: A mixture of benzaldoxime (100 mg), copper catalyst (10 mol-%), base (2.5 equiv.), and P_2S_5 (1 equiv.) in solvent (3 mL) was heated at 140-150 ^oC for12 h. [b] n.r.: no reaction

Table 3. Synthesis of Thioamide Derivatives



Entry	Aldoxime	Thioamide	Yield [%]
1	 **2a**	 **3a**	80
2	 **2b**	 **3b**	40
3	 **2c**	 **3c**	79
4	 **2d**	 **3d**	20
5	 **2e**	 **3e**	75
6	 **2g**	 **3g**	40

CONCLUSION

In conclusion, we have developed a one-step protocol for the direct transformation of aldoximes into thioamides in the presence of a copper catalyst. This reaction procedure is

very simple, economic and does not require any inert atmosphere to afford reasonable yield of the thioamides.

EXPERIMENTAL SECTION

General experimental details: All the substrates (Aldrich, Fluka, and Lancanster) were used as received. Other reagents were of AR grade. The extracts were dried over anhydrous Na_2SO_4. The IR spectra were scanned as films on a Perkin Elmer FT-IR model Impact 410 spectrometer. The ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ with a Bruker FT-NMR-400 MHz Spectrophotometer.

Typical Procedure for the Synthesis of 2a: To a reaction mixture of benzaldehyde (**1a**) (1 g, 9.4 mmol) in methanol-water (1:1), $NH_2OH.HCl$ (1 equiv.) and Na_2CO_3 (0.5 equiv.) was added. And the reaction mixture was left for overnight stirring at rt. The reaction progress was checked through TLC. Then, the organic layer was separated, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The procedure afforded a pure product in 99% yield.

Typical Procedure for the Synthesis of 3a: To a stirred reaction mixture of aldoxime (**2a**) (100 mg, 0.5 mmol), CuI (0.1 equiv.), and Et_3N (2.5 equiv.) in DMF (3 mL), the thionating reagent P_2S_5 (1 equiv.) was added. Then the reaction mixture was heated in oil bath at 140 ^oC for 12 hours. The completion of the reaction was checked by TLC. Then, the reaction mixture was cooled to room temperature and diluted with ethyl acetate and water. Then, the organic layer was separated, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was subjected to column chromatography on silica gel [ethyl acetate/petroleum ether (60–80 °C), 30%] to afford pure **3a** in 80% yield.

NMR SPECTRAL DATA

Benzothioamide **(3a)**: 3a was obtained following general procedure as a white crystalline solid. (86 mg, 80%): mp 142-143 °C ^1H NMR (400 MHz, $CDCl_3$) δ 7.90-7.87 (m, 2H, *J*=8 Hz), 7.55-7.51 (m, 1H, *J*=1.2 Hz), 7.45-7.41 (m, 2H, *J*=2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.9, 139.2, 132.0, 130.1, 128.5, 126.9, 77.3, 77.0, 76.7.

2-cholorobenzothioamide **(3b)**: 3b was obtained following general procedure as a blackish solid. (240 mg, 32%): mp 143.5-144.5 °C ^1H NMR (400 MHz, $CDCl_3$) δ 7.52-7.44 (m, 1H, *J*=8 Hz), 7.40 (s, 1H), 7.38-7.28 (m, 1H, *J*=8.8 Hz).

4-Methoxybenzothioamide **(3c)**: 3c was obtained following general procedure as an orange solid. (87 mg, 79%): mp 179-181 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (t, 2H, *J*=6.8 Hz), 7.59 (d, 1H, *J*=6.4 Hz), 7.282 (s, 1H), 7.135 (s, 1H), 6.91 (d, 2H, *J*=8.8 Hz), 3.88 (s, 3H).

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