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Green and efficient synthesis of propargylamines *via* A^3 coupling reaction using a copper (II)–thioamide combination

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Abstract

A one pot green three-component coupling reaction of aldehyde, phenylacetylene, and amine derivatives in the presence of copper (II)–thioamide combination as a novel and efficient heterogeneous catalyst under solvent–free conditions is reported. The catalyst displayed high activity and afforded the corresponding propargylamines in good to high yields. The key to this procedure was the generation of Cu (I) required for the A^3 coupling reaction, which was achieved by *in situ* reduction of Cu (II) using thiobenzanilide as reduction agent and ligand. The structure of the products was confirmed by ^{1}H NMR, ^{13}C NMR and EI-MS and comparison with authentic samples prepared by reported methods.

Keywords: Propargylamine; copper (II)–thioamide combination; heterogeneous catalyst; A^3 coupling reaction; green chemistry.

Introduction

As one of the prominent medicinal motifs, the propargylamine group featured in a large number of bioactive compounds would offer a wide range of activities, including anti-tumor, anti-oxidant, cardio-protective activity and many more [1-3]. The marketed drugs containing propargylamine moiety are known to have many neuroprotective activities such as anti–Parkinson, anti–Alzheimer, anti–Lewy body dementia, and anti–depressant activity (Figure 1) [4-8]. Furthermore, these compounds have been used as plant protective agents [9].

Propargylamines are also considered as one of the most important and versatile synthons in organic synthesis. They can be successfully transformed into various nitrogen–containing compounds, such as pyrroles, pyridines, piperidines, pyrrolidines, oxazoles, β–lactams, quinolones, imidazoles, and *N*–heterocyclic carbene complexes. Besides, they have been used as intermediates in the preparation of complex natural products, butenolides and oxotremorine analogues (Figure 2) [10-15].

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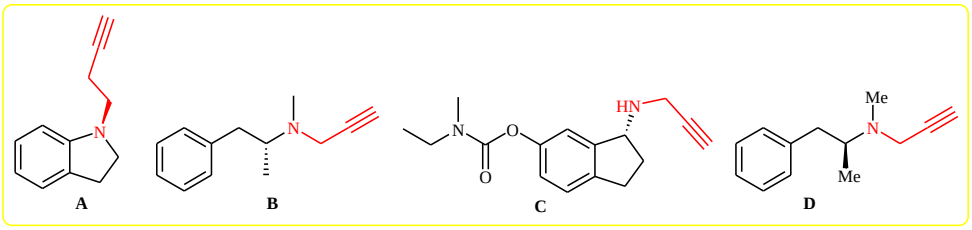


Figure 1. Some chemical structure of the marketed drugs containing propargylamine motif (Rasagiline A, Selegiline B, Ladostigil C, D–Deprenyl D)

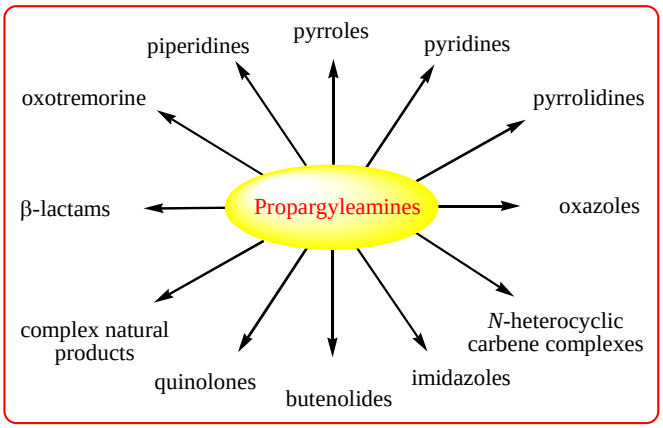
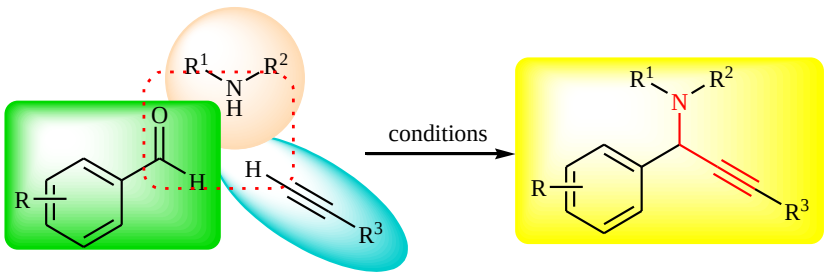


Figure 2. The main synthetic applications of propargylamines

Due to diversity of these analogs in the therapeutic response profile and widespread synthetic applications of them, many researchers were encouraged to improve the synthetic routes of this skeleton. In this regard, the A^3 coupling (Aldehyde, Alkyne, and Amine) has received much attention for the synthesis of various propargylamines through one–pot (multi–component reaction) from simple and commercially available starting materials (Scheme 1) [16].



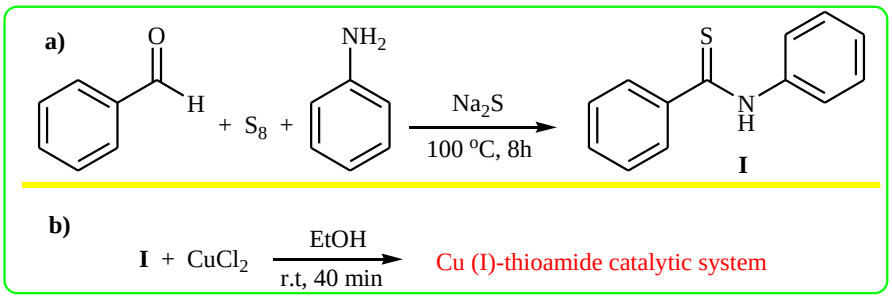
Scheme 1. Synthesis of propargylamines *via* A^3 coupling

A number of transition metal complxes has been found to efficiently catalyze the coupling reaction including Ag, Au, Ir, In, Hg, Cu, where copper has received much attention due to its efficiency and safety [17-20].

It should be noted that almost all of the studies for Cu–catalyzed A^3 coupling were proceeded by Cu (I). However, working with Cu (I) salt is problematic due to its general thermodynamic instability. Moreover, the protection of this center from

oxidation or disproportionation by coordination with ligands are tedious and expensive. It should also be noted that recycling and reusability of them are difficult because of their generally homogeneous nature.

Herein, we wish to report the synthesis of wide range of propargylamines using our novel heterogeneous copper (I)–thioamide catalytic system under solvent–free condition (Scheme 2).



Scheme 2. a) Preparation of thiobenzanilide **I** *via* Willgerodt–Kindler reaction; b) General procedure for the synthesis of copper (I)–thioamide catalytic system

Experimental

General

All the chemicals required for the synthesis of the propargylamines **4** were purchased from Sigma-Aldrich (St. Louis, MO, USA), Fluka (Neu-Ulm, Germany) and Merck (Darmstadt, Germany) companies and were used as received. The synthesized compounds **4** gave satisfactory spectroscopic data. A Bruker (DRX‑400 Avance) NMR was used to record the ^{1}H NMR and ^{13}C NMR spectra. All NMR spectra were determined in $CDCl_3$ at ambient temperature. Gas chromatography-mass spectrometry (GC-MS) (Agilent HP 6890, electron ionization (EI), 70 eV, HP-5 column (30 m × 0.25 mm × 0.2 μm), HP 5793 mass selective detector) was used to record the mass spectra. All the reactions were monitored by thin layer chromatography (TLC) carried out on silica gel with UV light and iodine, as detecting agents.

General procedure for the synthesis of copper (I)-thioamide catalytic system

$CuCl_2$ (2.0 mmol) was added into the solution of thiobenzanilide (2.0 mmol) in ethanol (1 mL) at room temperature. After 40 min a dark red precipitate which was observed was filtrated, washed with ethanol and dried at room temperature. The obtained precipitate is stable in air and insoluble in organic solvents, except DMSO and DMF.

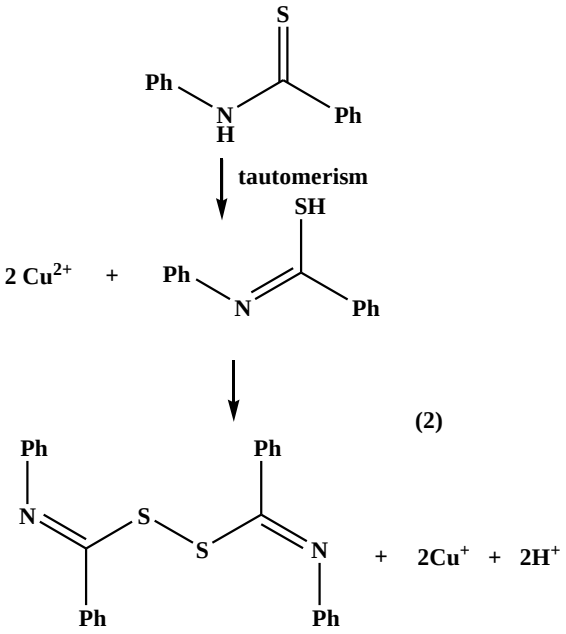
General procedure for synthesis of propargylamines 4

The reaction mixture of aldehyde **1** (1.0 mmol), secondary amine **2** (1.0 mmol), and phenylacetylene **3** (1.0 mmol) in the presence of 10 mg copper (I)–thioamide catalyst was stirred at 80 °C for 12 h without solvent. After completion of the reaction, as judged by TLC, dichloromethane (2 mL) was added to the mixture and the catalyst was recovered by filtration. The catalyst was reused in subsequent reaction without losing any significant activity. The mixture was concentrated under vacuum. The residue was purified by column chromatography (eluent: n–hexane/ethyl acetate 4:1). The structure of the products was confirmed by ^{1}H NMR, ^{13}C NMR and EI-MS and comparison with authentic samples prepared by reported methods (See electronic supporting information).

Results and discussion

The catalyst was easily prepared using reaction of $CuCl_2$ and thiobenzanilide presented in Scheme 2 [21, 22]. Organo-thiols and thiones can generally reduce copper(II) and, accordingly, disulfide compounds are formed according to the following equation (1) [23]:

It is conceivable that thiobenzanilide can exhibit thione-thiol tautomerism in the presence of Cu^{2+}, so the formation of the corresponding disulfide is possible. Acceleration of the A^3 coupling reaction using $CuCl_2$-thioamide combination supported the fact that copper (II) is reduced to copper (I). During this redox reaction, thiobenzanilide is oxidized to the corresponding disulfide according to the equation (2).



Equation 2. Oxidation of thiobenzanilide to corresponding disulfide using Cu (II)

Reduction of Cu^{2+} to Cu^{+} by thiobenzanilide is also consistent shown in the result obtained by ^1H NMR analysis of copper (I)-thioamide catalytic system in DMSO-d_6. ^1H NMR spectrum of complex bearing Cu^{2+} could not be obtained due to its paramagnetism properties. The ^1H NMR appearance of copper-thioamide catalyst revealed that a redox reaction takes place in the combination of $CuCl_2$ with thiobenzanilide in ethanol (electronic supporting information). The univalence of the copper ions in catalytic system was also confirmed by the measured diamagnetism. Unfortunately, all attempts to get single crystals of copper (I)-thioamide catalytic system for X-ray crystallography were failed due to its high insolubility. Energy-dispersive X-ray spectroscopy (EDS) was used for the chemical characterization of copper (I)-thioamide catalyst. EDS analysis exhibited the existence of chlorine atoms in catalytic system (electronic supporting information). CHN analysis exhibited 44.48 % C, 3.05 % H and 3.73 % N. Assignments of selected characteristic IR bands (4000-500 cm^{-1}) for thiobenzanilide and copper (I)-thioamide catalyst are given in supporting information (electronic supporting information). The positions

of bands provide significant hints regarding the bonding sites of the thiobenzanilide when complexed with copper (I). Thiobenzanilide can show thione-thiol tautomerism. The υ(S-H) band at 2550 cm^{-1} is absent in IR spectrum of thiobenzanilide but the υ(N-H) band is observed at 3418 cm^{-1}, indicating that thiobenzanilide exists in the thione rather than the thiol form in the solid state. The presence of nitrogen atom and the larger and less electronegative sulfur atom as soft donor enables the thioamides-NH to bind to a metal in different ways giving a variety of the polymeric complexes [24]. Our initial investigation on the A^3-coupling reaction focused on the effect of solvents for the reaction of benzaldehyde (1.0 mmol), morpholine (1.2 mmol), and phenylacetylene (1.0 mmol) in the presence of 10 mg of copper (I)–thioamide catalyst at reflux temperatures (Table 1). The outcome of the reaction was dependent on the nature of the solvent and temperature. It was observed that all the screened solvents afforded a low to moderate product yield after 12 h (Table 1, entries 1–5). The much better yield was obtained under solvent-free condition at 80 °C (Table 1, entry 6). Therefore, solvent–free condition was determined to be most effective for the generation of the desired product.

Table 1. Screening of various solvents for the A^3-coupling reaction between benzaldehyde, morpholine and phenylacetylene[a]

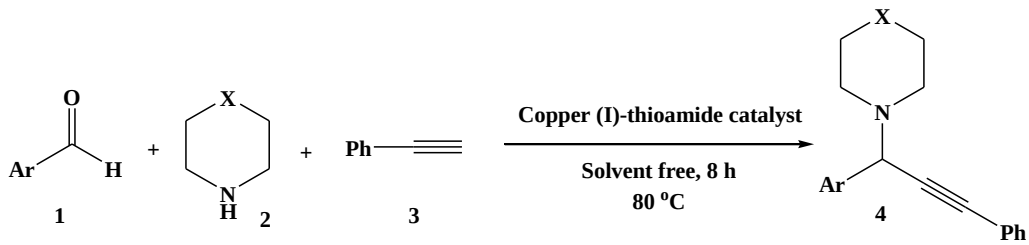
Entry	Solvent	Temperature (ºC)	Isolated yield (%)
1	H_2O	100	35
2	DMF	130	Trace
3	MeCN	65	50
4	THF	65	45
5	MeOH	65	70
6	Neat	80	85
7[b]	Neat	80	89

[a]Reaction conditions: benzaldehyde (1 mmol), morpholine (1 mmol), phenylacetylene (1 mmol), copper (I)–thioamide catalyst (10 mg), solvent 2 mL, 12 h. [b] morpholine (1.2 mmol)

Then, upon examination of catalyst loading we found that raising the catalyst loading from 10 mg to 20 mg did not change the product yield, but lowering the catalyst loading to 5 mg significantly reduced the isolated yield to 37%. When employing 1.2 equiv. of morpholine, the resulting propargylamine was obtained in only 89% yield after 12 h (Table 1, entry 7). The reason for this is not clear, but it is known that the amine plays two vital roles in the reaction: deprotonation of the presumed copper-coordinated phenylacetylene and nucleophile in the formation of the iminium intermediate (Scheme 3).

Following the optimized conditions, a variety of propargylamines were prepared from various aldehydes, secondary amines, and phenylacetylene using 10 mg catalyst under solvent-free condition at 80 ºC, and the results are summarized in Table 2.

Table 2. Green and efficient synthesis of a variety of propargylamines **4** using copper (I)–thioamide system



Entry	Ar	X	Product	Yield (%)[a]	[Ref.]
1	Ph	O	**4a**	85	[25]
2	4-Me-Ph	O	**4b**	72	[26]
3	4-OMe-Ph	O	**4c**	75	[25]
4	4-Cl-Ph	O	**4d**	90	[27]
5	3-NO_2-Ph	O	**4e**	77	[28]
6	2-OMe-Ph	O	**4f**	70	This work
7	2-Cl-Ph	O	**4g**	73	This work
8	2-OH-Ph	O	**4h**	72	[26]
9	Ph	CH_2	**4i**	91	[27]
10	4-Me-Ph	CH_2	**4j**	80	[27]
11	4-Cl-Ph	CH_2	**4k**	94	[27]
12	2-Cl-Ph	CH_2	**4l**	76	[27]

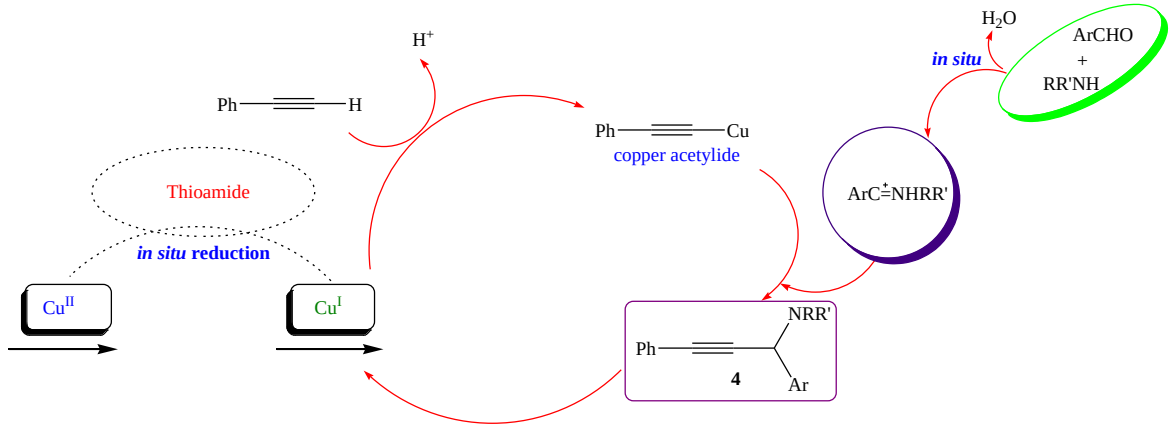
[a] Isolated yields

The reaction scope appears to be quite broad as electron donating and withdrawing groups were tolerated at various substitution sites of aldehydes (Table 2, entries 2–12). However, the aldehydes with electron donating group such as methyl, hydroxyl, and methoxy give lower yields as compared to benzaldehyde and aldehydes with electron–withdrawing group such as nitro and halogen. In the case of amines, morpholine (Table 2, entry 1–8) gives relatively lower yield as compared to piperidine (Table 2, entry 9–12).

The structures of the products were confirmed by EI–MS, ^{1}H NMR, and ^{13}C NMR spectroscopy (electronic supporting information). The ^{1}H NMR and ^{13}C NMR spectra of the product clearly indicated the formation of **4b**. The ^{1}H NMR spectrum of **4b** consisted of four lines for the aromatic protons at δ = 7.21–7.57 ppm, a singlet for the benzylic protons at δ = 4.81, two multiplets for protons of morpholine at δ = 2.68 and 3.80 ppm and a singlet at δ = 2.40 ppm for CH_3. The ^{1}H–decoupled ^{13}C NMR spectrum of **4b** showed 14 distinct resonances in agreement with the proposed structure, a resonance at δ = 21.2 ppm for CH_3, a resonance at δ = 49.9 ppm for methylene carbons of morpholine (N–CH_2), a resonance at δ = 61.8 ppm as benzylic carbon, a sharp resonance at δ

= 67.2 ppm for methylene carbons of morpholine (O–CH_2), two resonances at δ = 86.4 and 88.3 ppm for acetylene carbons and 8 distinct resonances for aromatic carbons between δ = 123.1–137.5 ppm. EI–MS mass spectrum of **4b** clearly showed the presence of the molecular ion ($M^{+\bullet}$, 291) with relative moderate abundance.

A possible mechanism for this copper (I)–thioamide catalyst multicomponent reaction was depicted in Scheme 3.



Scheme 3. Mechanism for copper (I)–thioamide–catalyzed synthesis of propargylamines

The reaction was initiated by the metalation of phenylacetylene **3** in the presence of Cu^+, resulting a copper (I)–acetylide. Condensation between aldehyde **1** and amine **2** generates a molecule of water and an iminium ion. Then the copper (I)–acetylide intermediate is added to the iminium ion to give the corresponding propargylamine **4** and regenerate the Cu (I) catalyst for a further sequence of reaction.

Reusability of the catalyst was investigated in the model reaction under the optimized reaction conditions. The catalyst was separated from the reaction mixture by simple filtration, washing with ethanol, and reused five times with a slight loss of the catalytic activity (Table 3).

Table 3. Reusability of the catalyst in the model

Entry	Fresh	Cycle 1	Cycle 2	Cycle 3	Cycle 4
Yield (%)	85	84	81	78	74

Conclusion

In summary, a very efficient method for the preparation of a variety of propargylamines was reported *via* the A^3–coupling reaction between benzaldehydes, amines and phenylacetylene in the presence of a cheap and easily recyclable heterogeneous copper(I)–thioamide catalyst under solvent-free conditions. The catalyst was easily prepared with the reaction of $CuCl_2$ and thiobenzanilide. The catalyst was collected easily by filtration and the reusability of it was successfully tested for five runs only with a very slight loss of catalytic activity. Further studies of applicability of the heterogeneous

copper(I)–thioamide catalyst for synthesis of useful organic compounds such as propargylamine-based sulfonamides are in progress.

Acknowledgements

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