A greener and sustainable approach towards the synthesis of propargylamine using multicomponent A³-coupling reaction

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ABSTRACT

The abundance of toxic contaminated effluents from the pharmaceutical industries and the serious risk of contamination of the aquatic systems were combined to provide strong motivating factors to tackle this environmental problem. Use of non-hazardous chemicals in aqueous medium is an interesting ecological alternative for the bulk production of important drugs and fine chemicals. Taking advantage of the remarkable ability of the selected catalytic systems, alternative sustainable methods have been exploited for the decontamination of industrial effluents and exhausts. In this work, we presented a newly developed metal-organic complex [Bis(picolinate-κ²N,O) Cu(II)] catalysed A³-coupling reaction in water which has established an excellent greener protocol to yield propargylamine. Low toxicity, easy access to active sites, high surface area, high thermal stability, recyclability of the catalyst, and easy way to separate the catalyst from the reaction mixture are the added advantage of this developed greener and sustainable protocol.


KEYWORDS

A³-coupling reaction
Propargylamine
Greener protocol
Sustainable chemistry
Metal-organic complex

Graphical Abstract

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Introduction

Development of multicomponent reaction through the sustainable and cost effective greener approach for the synthesis of biologically active compounds and fine chemicals have attracted a great deal of attention from the researchers [1]. The modern organic synthesis multicomponent reactions (MCR) are established as most efficient tools for developing a simple, cost efficient process, maintaining atom economy and the designing of straight forward reaction protocol [2–10]. Amongst the recently developed various methods established so far for the synthesis of bio-active compounds, A³-coupling reaction is one of the most fascinating approach. It is also well documented that three component A³-coupling reaction is one of the most important synthetic tools for the synthesis of various propargylamine through the C-H activation of terminal alkynes [11–16]. Propargylamines are widely utilized as a key intermediate for building various nitrogen containing heterocycles and biologically active compounds [17–20]. The amine functional group were used as a precursor to develop various important biologically active N-heterocycles such as, pyrrolo[1,2-α]-quinoline, quinolones, amino indolizine etc [21], compounds possessing a wide variety of biological and medicinal properties such as alzheimer [22], antiparkinson [23], and anti-apoptotic [24]. Due to their wide range of applications, development of a very simple, cost effective and sustainable protocol has always been a challenge for the researchers and as a consequence, variety of catalytic procedure has so far been reported for the synthesis of these important classes of amines, propargylamines. Various transition metal-based catalysts such as, NHC-Ag (I) complex [25a], AuBr₃ [25b], Fe₃O₄ nanoparticles [26], Ni-Y zeolite [27], Chitosan/Zn (NO₃)₂ composite [28a], silica-immobilized Cul [28b], InCl₃ [29], CoCl₂(PPh₃)₂ [30], [IrCl(cod)]₂ [31], BiCl₃ [32], CdI₂ [33], MnCl₂ [34], Hg₂Cl₂ [35] have reported so far for their synthesis and copper is the most commonly studied metal among the various metal catalyst applied for the A³-coupling reaction [36, 37]. However, homogeneous nature of the catalytic system has been the major drawback of their usage in practical application. Some of the heterogeneous catalytic system such as silica-immobilized Cul, [38], amberlyst A-21 supported Cul [39], lanthanum loaded CuO NPs [40], Cu-Ni bimetallic [41], copper ferrite NPs [42], graphene oxide-supported CuCl₂ [43], Cu (II) Schiff base complex immobilized on graphene oxide [44] have been reported so far. However, most of them suffer from several disadvantages including, low thermal stability, separation problem, significant leaching after several cycles of the reaction and the use of toxic solvents in most of the cases. A close observation of the results indicated a dire need of cleaner approach to enrich the scope and applicability of such reaction (A³-coupling) in the present context of establishing green and sustainable protocols. Therefore, improvement in the area of development of suitable catalyst, solvent, the reaction temperature, and reaction hours would certainly make the protocol much more applicable to accept it as a clean and green method for the synthesis of the versatile biological
precursor, propargylamine, over the existing methods. Furthermore, it is also apparent that, in line with the current trends in sustainable and green chemistry, copper-based heterogeneous catalytic reactions are reported in the literature. This area of research continues to evolve as a more suitable approach because of its crucial advantages such as the easy separation of products from catalyst, a high stability of the heterogeneous catalysts, and most importantly, their recyclability. In that aspect, protocols comprising heterogeneous copper catalysts employing C-C coupling reaction are certainly worth mentioning.

Keeping these views in mind we have synthesized a very specific organo-copper complex, and simultaneously applied it to establish a greener and efficient multicomponent A³-coupling reaction for the synthesis of propargylamine.

**Experimental**

**Materials and methods**

All the chemicals and solvents were purchased from the Sigma-Aldrich and Alfa aeser chemical suppliers. All the synthesized products were purified by column chromatography on 60-120 mesh silica gel (SRL, India). IR spectra were recorded on KBr disc for the compounds at the range of 4000-400 cm⁻¹ on Shimadzu FT-IR 8300 spectrometer. The ¹H and ¹³C NMR spectra were recorded on 400 MHz and 300 MHz Bruker avance FT-NMR spectrometer using CDCl₃.

**General procedure for synthesis of propargylamine**

A mixture of benzaldehyde (1 mmol), phenylacetylene (1 mmol), and morpholine (1 mmol) in 5 mL water was stirred at 80 °C and the progress of the reaction was monitored using the TLC. After completion of the reaction, the reaction mass cooled, then the solution was poured in 100 mL water and extracted with ethyl acetate, washed several time with water. The combined organic mixture was dried over anhydrous Na₂SO₄, concentrated and the residue was purified by column chromatography on silica gel 60-120 mesh using petroleum ether/ethyl acetate (95:5) as eluent to afford the pure product.

**4-(1,3-diphenylprop-2-ynyl)morpholine (3a)**

Brown oil, yield 95%, ¹H NMR (300 MHz, CDCl₃): δ 2.53 (s, 4H), 3.62 (s, 4H), 4.68 (s, 1H), 7.20-7.28 (m, 6H), 7.39-7.43 (m, 2H), 7.53 (d, J = 7.2 Hz, 2H). ¹³C NMR (300 MHz, CDCl₃): δ 26.4, 49.4, 61.6, 66.7, 84.6, 88, 117.6, 122.5, 127.3, 127.7, 127.8, 128.1, 131.3, 137.4.

**4-(3-phenyl-1-o-tolylprop-2-ynyl)morpholine (3b)**
White liquid, yield 96%, $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.37 (s, 3H), 2.52 (s, 4H), 3.56-3.60 (t, $J$ = 9.3, 4H), 7.09-7.11 (m, 3H), 7.20-7.22 (m, 3H), 7.40-7.43 (m, 2H), 7.58-7.60 (m, 1H). $^{13}$C NMR (300 MHz, CDCl$_3$): $\delta$ 18.6, 49.3, 59.3, 66.7, 84.6, 88.1, 122.6, 124.9, 127.3, 127.7, 127.8, 128.5, 130.2, 131.3, 135.3, 137.

4-(1-(4-methoxyphenyl)-3-phenylprop-2-ynyl)morpholine (3c)

Brown oil, yield 96%, $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.62 (s, 4H), 3.73 (s, 3H), 3.80 (s, 4H), 4.73 (s, 1H), 6.89 (d, $J$ = 9Hz, 2H), 7.31-7.33 (m, 3H), 7.49-7.55 (m, 4H). $^{13}$C NMR (300 MHz, CDCl$_3$): $\delta$ 49.3, 54.8, 60.9, 66.6, 84.8, 87.7, 113, 122.5, 127.7, 127.8, 129.2, 131.3, 158.7, 161.8.

4-(3-phenyl-1-p-tolylprop-2-ynyl)morpholine (3d)

White liquid, yield 96%, $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.40 (s, 3H), 2.66-2.67 (m, 4H), 3.77 (s, 4H), 4.79 (s, 1H), 7.22 (d, $J$ = 7.8 Hz, 2H), 7.35-7.37 (m, 3H), 7.54-7.56 (m, 4H). $^{13}$C NMR (300 MHz, CDCl$_3$): $\delta$ 20, 48.8, 60.7, 66.3, 84.5, 87.2, 122, 127.1, 127.2, 127.4, 127.8, 130.7, 133.7, 136.3, 161.8.

4-(1-(2-bromophenyl)-3-phenylprop-2-ynyl)morpholine (3e)

Brown oil, yield 90%, $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.66 (s, 4H), 3.68 (s, 4H), 5.06 (s, 1H), 7.12-7.17 (m, 1H), 7.22-7.31 (m, 4H), 7.48-7.59 (m, 3H), 7.73-7.75 (m, 1H). $^{13}$C NMR (300 MHz, CDCl$_3$): $\delta$ 49.7, 61.3, 67.1, 84.6, 88.6, 122.8, 125.2, 126.9, 128.3, 129.3, 130.6, 131.8, 133.3, 137.2.

4-(1-(naphthalen-3-yl)-3-phenylprop-2-ynyl)morpholine (3f)

Orange oil, yield 92%, $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.66 (s, 4H), 3.74 (s, 4H), 4.92 (s, 1H), 7.33-7.35 (m, 3H), 7.46-7.49 (m, 2H), 7.54-7.57 (m, 2H), 7.72-7.75 (m, 1H), 7.82-7.85 (m, 3H), 8.08 (s, 1H). $^{13}$C NMR (300 MHz, CDCl$_3$): $\delta$ 49.5, 61.7, 66.7, 84.5, 88.3, 122.5, 125.6, 126, 127, 127.1, 127.5, 127.6, 127.8, 131.3, 132.6, 134.9.

4-(1-(naphthalen-8-yl)-3-phenylprop-2-ynyl)morpholine (3g)

Orange oil, yield 93%, $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.68 (s, 4H), 3.65 (s, 4H), 5.40 (s, 1H), 7.29 (m, 3H), 7.39-7.52 (m, 5H), 7.77-7.92 (m, 3H), 8.35 (d, $J$ = 7.8 Hz, 1H). $^{13}$C NMR (300 MHz, CDCl$_3$): $\delta$ 49.9, 60.2, 67.2, 85.1, 89.1, 123.1, 124.8, 125.7, 126, 127.2, 128.3, 128.4, 128.6, 129, 131.7, 131.9, 133.2, 134.1.

4-(3-phenyl-1-(thiophen-2-yl)prop-2-ynyl)morpholine (3h)
Brown oil, yield 87%, $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.68 (s, 4H), 3.76 (s, 4H), 6.97-6.98 (m, 1H), 4.99 (s, 1H), 7.24-7.34 (m, 5H), 7.51 (s, 2H). $^{13}$C NMR (300 MHz, CDCl$_3$): $\delta$ 49.6, 57.8, 67.1, 84.2, 87.5, 122.6, 125.7, 126.3, 126.3, 128.3, 128.4, 131.8, 142.8.

4-(1-(4-fluorophenyl)-3-phenylprop-2-ynyl)morpholine (3i)

Brown oil, yield 85%, $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.60-2.62 (m, 4H), 3.71-3.73 (m, 4H), 4.75 (s, 1H), 7.01-7.07 (m, 2H), 7.31-7.33 (m, 3H), 7.49-7.52 (m, 2H), 7.58-7.59 (m, 2H). $^{13}$C NMR (300 MHz, CDCl$_3$): $\delta$ 49, 57.3, 66.3, 81.4, 90.1, 121.9, 123.8, 127.9, 128.1, 128.3, 129.6, 130.9, 131.3, 131.6, 149.4.

4-(1-(2-nitrophenyl)-3-phenylprop-2-ynyl)morpholine (3j)

Brown oil, yield 84%, $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.43 (s, 2H), 2.62 (s, 2H), 3.63 (s, 4H), 5.65 (s, 1H), 7.26-7.56 (m, 7H), 7.71 (d, $J$ = 7.5 Hz, 1H), 7.95 (d, $J$ = 7.2 Hz, 1H). $^{13}$C NMR (300 MHz, CDCl$_3$): $\delta$ 49, 57.3, 66.3, 81.4, 90.1, 121.9, 123.8, 127.9, 128.1, 128.3, 129.6, 130.9, 131.3, 131.6, 149.4.

1-(3-phenyl-1-p-tolylprop-2-ynyl)piperidine (3k)

Pale yellow oil, 94%, $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.33 (s, 2H), 1.47-1.49 (m, 4H), 2.24 (s, 3H), 2.45 (s, 4H), 4.65 (s, 1H), 7.05 (d, $J$ = 7.2 Hz, 2H), 7.19-7.20 (m, 2H), 7.40-7.42 (m, 4H). $^{13}$C NMR (300 MHz, CDCl$_3$): $\delta$ 20.6, 24, 25.7, 50.2, 61.7, 85.9, 87.2, 123, 127.5, 127.7, 128, 128.3, 131.3, 135.2, 136.5.

1-(3-phenyl-1-o-tolylprop-2-ynyl)piperidine (3l)

Pale yellow oil, yield 93%, $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.33 (s, 2H), 1.47-1.49 (m, 4H), 2.24 (s, 3H), 2.45 (s, 4H), 4.65 (s, 1H), 7.06 (d, $J$ = 7.2 Hz, 2H), 7.19-7.20 (m, 3H), 7.40-7.42 (m, 4H). $^{13}$C NMR (300 MHz, CDCl$_3$): $\delta$ 20, 25.1, 28.6, 49.6, 61.1, 85.3, 86.5, 122.4, 126.9, 127.2, 127.4, 127.7, 130.7, 134.6, 135.9.

1-(1-(4-fluorophenyl)-3-phenylprop-2-ynyl)piperidine (3m)

Brown oil, yield 88%, $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.43-1.59 (m, 6H), 2.53 (s, 4H), 4.76 (s, 1H), 7.00-7.05 (m, 2H), 7.31-7.32 (m, 3H), 7.49-7.51 (m, 2H), 7.57-7.61 (m, 2H). $^{13}$C NMR (300 MHz, CDCl$_3$): $\delta$ 23.3, 25.6, 49.5, 60.5, 84.6, 87, 113.5, 113.8, 127, 127.1, 127.8, 130.6, 133.3.

1-(1,3-diphenylprop-2-ynyl)piperidine (3n)

Pale yellow oil, yield 96%, $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.32-1.64 (m, 8H), 2.60-2.62 (m, 4H), 4.85 (s, 1H), 7.29-7.47 (m, 7H), 7.56-7.71 (m, 3H), 7.85-7.91 (m, 2H). $^{13}$C NMR (300 MHz, CDCl$_3$) $\delta$ 25.7, 29.1, 50.2, 61.9, 85.6, 87.3, 121.7, 122.9, 128.4, 130, 131.3, 132.2, 138.2, 144.3.
2-(3-phenyl-1-(piperidin-1-yl)prop-2-ynyl)phenol (3o)

Brown oil, yield 87%. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.51 (s, 2H), 1.67 (s, 4H), 2.70-2.73 (m, 4H), 5.08 (s, 1H), 6.83-6.87 (m, 2H), 7.18-7.25 (m, 1H), 7.34-7.38 (m, 3H), 7.51-7.57 (m, 3H). $^{13}$C-NMR (300 MHz, CDCl$_3$): $\delta$ 24, 26, 50, 61, 82.3, 89.8, 116.3, 119, 121.3, 122.6, 128.4, 128.4, 128.5, 129.3, 131.9, 157.6.

4-benzyl-1-(1,3-diphenylprop-2-ynyl)piperidine (3p)

Pale yellow, yield 89%. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.43-1.47 (m, 1H), 1.50-1.53 (m, 1H), 1.59-1.67 (m, 2H), 1.75-1.78 (m, 1H), 2.21-2.27 (m, 1H), 2.53-2.61 (m, 3H), 2.72-2.75 (m, 1H), 3.02-3.05 (m, 1H), 4.89 (m, 1H), 7.19-7.44 (m, 8H), 7.31-7.34 (m, 3H), 7.56-7.58 (m, 2H), 7.69-7.71 (m, 2H). $^{13}$C-NMR (400 MHz, CDCl$_3$): $\delta$ 32.1, 37.5, 42.8, 46.9, 52.2, 61.6, 85.5, 87.5, 122.8, 125.3, 127.1, 127.6, 127.7, 127.8, 128.1, 128.7, 131.4, 138.1, 140.4.

4-(1,5-diphenylpent-2-ynyl)morpholine (3q)

Brown oil, yield 86%. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.35-2.46 (m, 4H), 2.58-2.62 (m, 2H), 2.84-2.88 (m, 2H), 3.61-3.68 (m, 4H), 4.45 (s, 1H), 7.03-7.30 (m, 8H), 7.37-7.45 (m, 2H). $^{13}$C-NMR (400 MHz, CDCl$_3$): $\delta$ 20.5, 29.3, 34.8, 49.3, 61.2, 66.7, 87.3, 125.9, 127.1, 127.6, 127.8, 128, 128.1, 128.4, 137.8, 140.2.

2-(1-benzylpiperidin-1-yl)-3-phenylprop-2-ynyl)phenol (3r)

Yellow viscous liquid, yield 85%. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.26-1.48 (m, 2H), 1.56-1.81 (m, 3H), 2.33-2.40 (m, 1H), 2.52-2.54 (m, 2H), 2.65-2.74 (m, 2H), 3.00-3.04 (m, 1H), 5.10 (s, 1H), 6.82-6.86 (m, 2H), 7.10-7.34 (m, 9H), 7.49-7.55 (m, 3H). $^{13}$C-NMR (300 MHz, CDCl$_3$): $\delta$ 31.9, 32.5, 37.7, 42.9, 46.4, 52, 60.7, 89.9, 116.4, 119.1, 121.3, 122.5, 125.9, 128.2, 128.4, 128.6, 129.1, 129.4, 131.9, 140.3, 157.6.

2-(3-phenyl-1-(pyrrolidin-1-yl)prop-2-ynyl)phenol (3s)

Pale yellow semisolid, yield 90%. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.87-1.89 (m, 4H), 2.78-2.88 (m, 4H), 5.29 (s, 1H), 6.82-6.87 (m, 2H), 7.19-7.27 (m, 1H), 7.34-7.37 (m, 3H), 7.51-7.54 (m, 3H). $^{13}$C-NMR (300 MHz, CDCl$_3$): $\delta$ 23.8, 48.9, 57.1, 83, 89, 116.2, 118.9, 122.2, 122.6, 127.8, 128.4, 128.5, 128.8, 129.9, 131.9, 157.6.

1-(1-phenylpent-1-yn-3-yl)pyrrolidine (3t)
Light brown viscous liquid; yield 75%; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.06-1.10 (m, 3H), 1.69-1.80 (m, 5H), 2.69-2.78 (m, 5H), 3.61 (s, 1H), 7.25-7.29 (m, 3H), 7.41-7.43 (m, 2H). $^{13}$C-NMR (400 MHz, CDCl$_3$): $\delta$ = 10.06, 23.05, 27.72, 49.40, 56.47, 84.93, 87.58, 122.98, 127.85, 129.06, 131.27.

1-(1-phenylnon-1-yn-3-yl)pyrrolidine (3u)

Pale yellow oil, yield 70%, $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.30-1.37 (m, 3H), 1.44-1.49 (m, 5H), 1.53-1.59 (m, 2H), 1.68-1.69 (m, 2H), 1.71-1.75 (m, 4H), 1.99 (s, 1H), 2.68-2.77 (m, 4H), 3.67-3.69 (m, 1H), 7.41-7.42 (m, 2H), 7.25-7.28 (m, 3H). $^{13}$C-NMR (400 MHz, CDCl$_3$): $\delta$ 13.6, 22.1, 23, 26.2, 28.6, 31.3, 34.6, 49.2, 54.7, 84.8, 87.8, 123, 127.3, 127.7, 131.2.

1-(1-(2-chlorophenyl)-3-phenylprop-2-ynyl)piperidine (3v)

Brown oil, yield 87%, $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.52-1.54 (m, 2H), 1.66-1.68 (m, 4H), 2.73 (s, 4H), 5.22 (s, 1H), 7.14-7.60 (m, 6H), 7.67-7.76 (m, 2H), 7.86-8.01 (m, 1H). $^{13}$C NMR (300 MHz, CDCl$_3$): $\delta$ 25.7, 29.2, 50.3, 58.9, 85.4, 87.3, 122.8, 125.7, 126.7, 127.8, 128.9, 129.3, 130.1, 131.3, 134.3, 136.12.

Figure 1. Single crystal X-ray analysis

Figure 2. Packing diagram of the synthesized catalyst
**Synthesis of Copper complex**

The copper (II) complex [45] was synthesized using a typical hydrothermal reaction. 1 mmol (0.123 g) pyridine-2-carboxylic acid, 1 mmol (0.21 g) trimesic acid and 1 mmol (0.242 g) of copper nitrate dihydrate was grinded in an agate motor and pastel. The blue colored mass obtained was then carefully transferred in a 10 mL teflon lined stainless steel autoclave and 5 mL of distilled water was added. The reaction mixture was stirred for 30 min with the help of magnetic stirrer to get a suspension. It was then heated in an automated hot air oven at a temperature of 150 °C for 48 h. The autoclave was then cooled to room temperature and the obtained product was filtered, washed with ethanol and water to remove the impurities in the compound. The compound was then dried over the vacuum pump.

**Results and Discussion**

*Characterization of copper (II) complex*

The copper (II) complex was characterized using various analytical techniques including, single crystal X-ray diffraction analysis, field emission scanning electron microscope (FE-SEM), and Fourier-transform infrared spectroscopy (FT-IR). The synthesized blue coloured copper (II) complex was air stable and has the melting point of above 300 °C. Single crystal analysis of the complex revealed that, the complex was crystallized in monoclinic crystal system with space group P 121/c1. The crystal structure and the packing of the complex are demonstrated in Figure 1 and Figure 2, respectively.

*FE-SEM analysis*

The field emission scanning electron microscopy (INSPECT F-50, FEI, Netherland) analysis was carried out to analyze the morphology of the synthesized copper (II) complex. From the electron micrograph of the complex, it is clear that the crystals have rod like morphology having several millimeters in length and thickness of 0.6-1 µm. As seen in the SEM micrograph of the copper (II) complex (Figure 3), the complex has same morphology and the bulk of the crystal has rectangular morphology or squared cross section. It is also evident from the ruptured crystal that the single crystals are composed of long filamentous grains running along the length of the crystals.

*FT-IR analysis*

The FT-IR spectra of the synthesized copper (II) complex showed peaks (ν/cm⁻¹) at 3091 (m), 1718 (s), 1599 (s), 1320 (s), 471 (w), 423 (w) and all these data mathes well with the earlier reported complex [45].
Figure 3. SEM image of the synthesized catalyst
In order to explore the catalytic activity of the newly developed greener catalyst, we put this in A3-coupling reaction with benzaldehyde (1 mmol), phenylacetylene (1 mmol) and morpholine as a model reaction under reflux using water as solvent. The reaction was completed in 8 h with a 95% yield of the desired product (Table 1, entry 6). However, when the same reaction was attempted under the similar condition in the absence of catalyst we did not get the desired product. Therefore, we can conclude that the reaction did not occur in absence of catalyst (Table 1, entry 1).

**Table 1.** Optimization of reaction parameters for the synthesis of propargylamine derivatives

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<td>8</td>
<td>80</td>
<td>DMF</td>
<td>86</td>
</tr>
<tr>
<td>16</td>
<td>10</td>
<td>8</td>
<td>80</td>
<td>Ethanol</td>
<td>87</td>
</tr>
<tr>
<td>17</td>
<td>10</td>
<td>24</td>
<td>RTc</td>
<td>Water</td>
<td>NR</td>
</tr>
</tbody>
</table>

*a* Reaction conditions: Benzaldehyde (1 mmol), phenylacetylene (1 mmol), morpholine (1 mmol), Copper catalyst (10 mg) at different temperatures and solvent  

b* Isolated yields  
c* Room temperature reaction

Therefore, to optimize the protocol, the model reaction was repeated with varying amount of the synthesized copper catalyst (Table 1) and out of all attempts we established that 10 mg of the catalyst (per mmol of the reactants) yielded the best result. We also tried various solvents including, DCM, DMF, toluene, DMSO, however could not beat the superiority of water as solvent.
Thus, the fortunately water was established as the optimal medium of the reaction. The reaction was also carried out in solvent free condition which also afforded the corresponding product but with only moderate yield (Table 1, entry 3). Further, to optimize the temperature, the model reaction was carried out at 50, 60, 70, 80, and 90 °C. Among them, the best yield was obtained at 80 °C (Table 1, entry 6). As seen in Table 1, yields were gradually increased with enhancing the temperature and the best result was obtained at 80 °C. At a temperature beyond 80 °C the increase of yield was not considerable and as a result, 80 °C was taken as an optimal temperature. The reaction was also tried at room temperature and even after 24 h of reaction we failed to isolate minimum yield of the product (Table 1, entry 17).

With this optimized condition we also carried out the same reaction by using the various amount of catalyst viz., 2, 4, 6, 8, 10, 12, and 14 mg. We found that 10 mg catalyst (per mmol of the reactants) was sufficient for the complete conversion of the reaction to the desired product (Figure 4). Further increase in the amount of catalyst did not improve the yield of the product considerably. With this optimized greener and optimized reaction condition we performed the reaction with various substituents (Table 2). To investigate the generality and scope of the catalytic activity of the synthesized catalyst in A3-coupling reaction, we carried out the reaction with a variety of aldehydes and terminal alkynes with different secondary amines. Both the electron donating/electron with drawing groups were employed with secondary amine. Aldehyde with electron donating groups afforded the desired product with high yield which might be due to the increased electron density in the aldehyde nucleus and thereby facilitating reaction faster (Table 2, entries 1-22). Bromo, chloro, and fluorobenzaldehydes were also tried and afforded excellent yields and the order of reactivity of aromatic halo aldehyde was –Br>–Cl>–F (Table 2, entries 5, 9, 13, 22). Aldehyde with electron withdrawing group such as –NO2 was needed more time to complete and afforded low yield of the product (Table 2, entry 10). However, hetero aldehyde provided with good yield of the product (Table 2, entry 8). The above protocol was also examined with aliphatic aldehydes (Table 2, entries 20, 21), which yielded the corresponding product in good yield. Napthaldehydes were tried to determine the substrate scope of this reaction and the results afforded the desired product in good yield (Table 2, entries 6 and 7). As seen in Table 2, it is obvious that the newly developed greener catalyst may direct the A3-coupling reaction for a wide range of substrate applicability for the synthesis of the propargylamine derivatives.

A plausible mechanism to access propargylamine involving aldehyde, phenylacetylene and morpholine at the presence of the synthesized catalyst is depicted in Scheme 1. It is assumed that, the reaction initiated by the nucleophilic attack of the amine to the activated electrophilic carbon of the aldehydic group, followed by removing the H2O molecule to yield the iminium ion [46, 47].
Table 2. Substrate scope of amines and aldehydes for the synthesis of Propargylamine

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Amine</th>
<th>Acetylene</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CHO</td>
<td>O</td>
<td></td>
<td><img src="image" alt="Product 3a" /></td>
<td>8</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3a</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>H&lt;sub&gt;3&lt;/sub&gt;C-CHO</td>
<td>O</td>
<td></td>
<td><img src="image" alt="Product 3b" /></td>
<td>8</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3b</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>CHO</td>
<td>O</td>
<td></td>
<td><img src="image" alt="Product 3c" /></td>
<td>8</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3c</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>CHO</td>
<td>O</td>
<td></td>
<td><img src="image" alt="Product 3d" /></td>
<td>8</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3d</td>
<td></td>
</tr>
</tbody>
</table>

R = -H, -CH₃, -OCH₃, -OH, -F, -Cl, -Br, -NO₂, etc.
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**Scheme 1.** Proposed mechanism of $A^3$-coupling reaction
Simultaneously, the catalytically activated C-H bond of the phenylacetylene formed the active acetylidine complex [46, 47]. Finally, the activated acetylidine complex was added with the iminium ion to yield the corresponding propargylamine.

The comparison as depicted in Table 3, clearly indicates that the developed catalyst with significant TOF and TON value (entry 3) together with its calculated atom economy (93.89%) established the protocol as a greener and sustainable approach.

**Table 3.** Comparison of conventional Cu(II) catalytic systems with the newly developed catalyst for the synthesis of propargylamine at 80 °C

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Mol% (Cu)</th>
<th>TOF (h⁻¹)</th>
<th>TON</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(II)-MOF</td>
<td>3.0</td>
<td>16.33</td>
<td>32.67</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>CMC-Cu</td>
<td>5.0</td>
<td>2.1</td>
<td>18</td>
<td>37</td>
</tr>
<tr>
<td>3</td>
<td>[Bis(picolinate-κ²N:O)copper(II)]</td>
<td>1.37</td>
<td>86.58</td>
<td>692.70</td>
<td>Present work</td>
</tr>
</tbody>
</table>

**Figure 4.** Recycling of [Bis (picolinate-κ²N:O)copper(II)]di(benzene1,3,5-tricarboxylic acid)

**Conclusions**

In this work, the synthesized copper catalyst was applied in a greener and sustainable version of multicomponent A³-coupling reaction of aldehyde, amine and terminal alkynes in water to obtain the desired product in good yield with excellent TOF, TON and atom economy. The recyclability of the
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A synthesized catalyst was found to be capable up to fifth run without any aggregation and significant metal leaching. The catalyst was also recovered easily after the completion of the reaction.

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Disclosure Statement

No potential conflict of interest was reported by the authors.

Supporting Information

Additional supporting information related to this article can be found, in the online version, at DOI: http://dx.doi.org/10.22034/ajgc.2021.113192.

References

[22]. Bolea I., Gella A., Unzeta M.* J. Neural Transm.*, 2013, **120**:893
[30]. Chen W.W., Bi H.P., Li C.J. *Synlett.*, 2010, **3**:0475
[33]. Raghuvanshi D.S., Singh K.N.* Synlett.*, 2011, **3**:0373
[34]. Afraj S.N., Chen C., Lee G.H. *RSC Adv.*, 2014, **4**:26301
[38]. Likhar P.R., Roy S., Roy M., Subhas M.S., De M.L., Kantam R.L. *Synlett.*, 2007, 2301


[41]. Katkar S.V., Jayaram R.V. *RSC Adv.*, 2014, 4:47958


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