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Copper(II) Nitrate Catalyzed Azide–Alkyne Cycloaddition Reaction: Study the Effect of Counter Ion, Role of Ligands and Catalyst Structure

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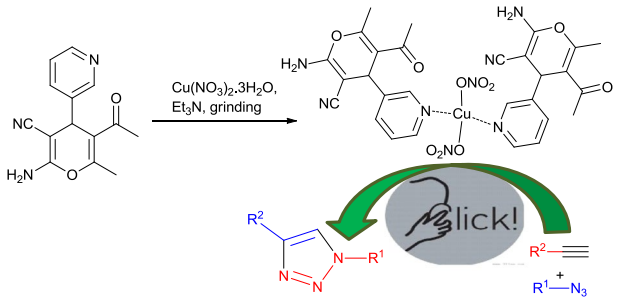
Abstract
For the first time, CuAAC reaction catalyzed by copper(II) nitrate and counter ion effect of various copper(II) salts are reported. Use of a novel copper complex **1**, derived from the reaction of copper(II) nitrate with 5-acetyl-2-amino-6-methyl-4-(pyridin-3-yl)-4*H*-pyran-3-carbonitrile, facilitated the CuAAC reaction at room temperature with a catalyst loading as low as 1 mol% within a very short reaction time.

Graphical Abstract



Keywords Click reaction · Copper nitrate · 5-Acetyl-2-amino-6-methyl-4-(pyridin-3-yl)-4*H*-pyran-3-carbonitrile · Copper(II) nitrate pyridine complex · Counter ion effect

1 Introduction

Compounds containing the triazole functionality have been known to exhibit a range of biological functions including antitumor, antibacterial, antiparasitic and antiviral activity. Interestingly, triazole moiety has similarities with the ubiquitous amide moiety found in nature, but unlike the amides, it is not susceptible to cleavage. Additionally, it is nearly impossible to oxidize or reduce triazoles and are inert towards biological molecules and aqueous environments which allows the use of the Huisgen 1,3-dipolar cycloaddition in target guided synthesis and activity-based protein profiling [1, 2].

The application of copper catalysts in click reactions stands out as a latest success of organometallic chemistry for the synthesis of 1,4-disubstituted triazoles in contrast to the uncatalyzed reaction via Huisgen reaction which provides both 1,4 and 1,5-regio-isomers at a very slow rate. The use of copper catalysts accelerates the rate of the reaction by 10^7 times and enables the reaction to perform in aqueous media with high yield and regioselectivity [3, 4]. The fact that Cu(I) is the active form of the catalytic systems, a range of catalytic systems [5–8] including the photochemical routes [9–12] have been developed over the last decade to tie

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over the instability of the catalyst. As a result, the emphasis has shifted to Cu(II) catalysts which can be converted to Cu(I) systems in the presence of a sacrificial reducing agent such as sodium ascorbate. However, most of Cu(II)–sodium ascorbate systems require various additives such as *N*-containing ligands [13], phase transfer catalysts [1], and acids [14]. Additionally, the use of copper(II) salts directly in the reaction creates the chance of metal contamination with the end triazole product to lower the yield. Nevertheless, the mechanism of click reaction involves multiple reversible steps involving coordination complexes of copper(I) acetylides of varying nuclearity. Therefore, a proper understanding on controlling the reaction dynamics is of paramount importance to achieve a productive catalytic cycle. Therefore, ligand designing is an important part for subtle control of the ligands over the metal centres to which they are coordinated.

Nature of the copper counter ion has dramatic effect on the rate and efficiency of the reaction. As Hein and Fokin [15] noted, the cuprous iodide catalyzed click reaction takes nearly 100 min for full conversion, while the same reaction completes within minutes with weakly coordinated copper tetrafluoroborate. Surprisingly, in spite of being the least expensive among the copper salts, copper nitrate have not found application in click reaction. Given the fact that, a nitrate counterion is more weakly coordinating ion toward copper(II) than the halide [16] ions, it can in principle work as better salt for click reaction. Moreover, the molecular structure of copper nitrate, where the copper ion is sandwiched between the planes of nitrate group, tends to reduce intermolecular forces, a property that may help in avoiding metal contamination in triazole end products observed in commonly used copper salts. In order to prove our contention, we planned to explore copper(II) nitrate as a catalyst for click reaction and its catalytic behaviour in the presence of various commonly used ligands. This study led to development of a novel Cu(II) nitrate pyridine complex–sodium ascorbate system for Click reaction which does not require any additives (Scheme 1).

2 Experimental Section

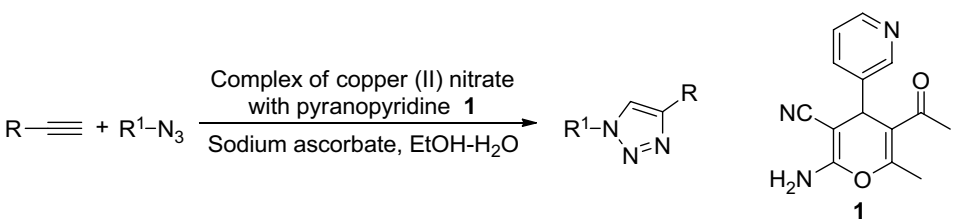
2.1 Materials and Instruments

The chemicals and reagents were available commercially and that were used without further purification. The products were characterized by IR, ^{1}H NMR, ^{13}C NMR, Mass spectroscopy and elemental analysis. The IR spectra were recorded on a Perkin Elmer spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained on a Bruker AC-400 using $CDCl_3$ as solvent and TMS as internal standard, unless otherwise stated. The mass spectra were obtained from Waters ZQ 4000 mass spectrometer by the ESI method, and the elemental analyses of the complexes were performed on a Perkin–Elmer-2400 CHN/S analyzer. Absorption spectra were obtained at room temperature using a Perkin-Elmer Lambda 25 UV–Vis spectrophotometer. The fluorescence measurement was carried out using HITACHI F4500 spectrophotometer. X-band EPR spectra at room temperature and at variable temperature were recorded from powdered sample and from DMSO solution on a Varian E-112 ESR Spectrometer using TCNE (g = 2.0027) as an internal standard. Room temperature magnetic susceptibility measurements were made on Sherwood Magnetic Susceptibility Balance MSB-Auto. SEM was carried out with JEOL JSM-6360 and EDAX was done with Oxford INCA 350 EDS.

2.2 Synthesis of Acetyl-2-amino-6-methyl-4-(pyridin-3-yl)-4*H*-pyran-3-carbonitrile

To a solution of pyridine-3-carbaldehyde (0.535 g, 5 mmol) and malononitrile (0.330 g, 5 mmol) in ethanol (50 mL), were added acetylacetone (0.5 g, 5 mmol) and Amberlyst A21 (30 mg/mmol). As the reaction progressed, precipitation of the product was observed. Upon stirring at room temperature for a specified time, the reaction underwent to completion as supported by TLC study. Warm ethanol (60 °C) was added to dissolve the solid product and filtered. The residue of Amberlyst A21 was washed thoroughly with warm ethanol. The combined ethanolic solution was concentrated and allowed to stand in a refrigerator to get pure crystalline product. Yield: 1.083 g (85%); white crystals;

Scheme 1 Copper(II) nitrate pyridine complex catalysed click reaction



m. p.: 163–164 °C; IR (KBr): 3356, 2190, 1686 $cm^{-1;}$ ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.93 (s, 3H, $\underline{H}_3C$–C=C–), 2.10 (s, 3H, $\underline{H}_3C$–CO–C=C–), 4.36 (s, 1H, –C$\underline{H}C_5H_4N$), 6.38 (s, 2H, NH_2), 7.18–7.21 (m, 1H), 7.39 (d, $J = 8$ Hz, 1H), 8.25–8.28 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.7 ($H_3\underline{C}$–C=C–), 30 ($H_3\underline{C}$–CO–C=C–), 36.2 (–$\underline{C}HC_5H_4N$), 56.8 (=$\underline{C}$–CN), 114.4 (H_3C–CO–$\underline{C}$=C–), 119.6(CN), 123.9 (C-5 of –C_5H_4N), 134.8 (C-1 of –C_5H_4N), 140 (C-6 of –C_5H_4N), 148.1 (C-4 of –C_5H_4N), 148.3 (C-2 of –C_5H_4N), 155.8 (H_3C–$\underline{C}$=C–), 158.4 (=$\underline{C}$–NH_2), 197.9 (C=O); ESI–MS (*m*/*z*): 256 $(M+H)^+$, 278 $(M+Na)^+$; Elemental Anal. for $C_{14}H_{13}N_3O_2$: Calcd. C 65.87, H 5.13, N 16.46 Observed C 65.78, H 5.15, N 16.12.

2.3 Synthesis of the Copper(II) Nitrate Pyridine Complex (1)

A mixture of 5-acetyl-2-amino-6-methyl-4-(pyridin-3-yl)-4*H*-pyran-3-carbonitrile (0.255 g, 1 mmol), $Cu(NO_3)_2{\cdot}3H_2O$ (0.5 equiv.) and Et_3N (0.5 mmol) was ground in mortar with pestle at room temperature. Within 20 min of grinding, formation of a melt was observed which got converted to a reddish brown colored solid mass after another 10 min. The solid mass was heated at 60 °C for 2 h and washed with 30% ethyl acetate–hexane mixture and finally dried over anhydrous $CaCl_2$ in a desiccator. Finally it was characterized by IR, UV–Vis spectroscopy, Fluorescence spectroscopy, EPR spectroscopy, ESI–MS analysis, magnetic susceptibility measurement, SEM, energy dispersive X-ray (EDX) and elemental analyses. M. p.: 298–299 °C; IR (KBr): 3250, 2196, 1675, 1634, 1482, 1432, 1297, 1113, 486 cm^{-1}; ESI–MS (*m*/*z*): 698 $(M+H)^+$, UV/Vis (MeOH) λ_{max}/nm: 260, 301, 359, 510. Magnetic Moment (B.M): 1.79. Elemental analysis for $C_{28}H_{26}N_8O_{10}Cu$: Calculated C 48.17, H 3.75, N 16.05; Observed C 48.21, H 3.68, N 16.15.

2.4 Typical Procedure for CuAAC

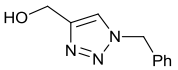
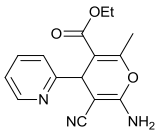
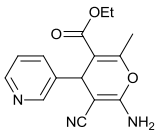
A 20-mL round-bottomed flask equipped with a magnetic stirrer was charged with benzyl azide (0.133 g, 1 mmol), phenyl acetylene (102 g, 1 mmol), and the copper(II) nitrate pyranopyridine complex **1** (1 mol%). A solution of sodium ascorbate (0.5 equiv.) in 1:1 ethanol–water mixture (6 mL) was added into it and stirred at room temperature for 10 min. After completion of the reaction, as evident from TLC, ethanol was removed in a rotavapor under reduced pressure and the aqueous solution was extracted with ethyl acetate (3 × 10 mL). The organic part was dried over Na_2SO_4 and the solvent was removed under reduced pressure to obtain the triazole derivative **3a** in 94% yield (0.221 g) as white solid with excellent purity. m.p.: 122–123 °C; IR (KBr): 3322, 3093, 3056, 1613, 1478, 1101 $cm^{-1;}$ ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.47 (s, 2H, –CH_2–), 7.22–7.31 (m, 8H), 7.58 (s, 1H), 7.71 (d, $J = 7.2$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 54.2, 119.6, 125.4, 125.7, 128.1, 128.2, 128.3, 128.5, 128.6, 128.8, 128.8, 129.1, 130.5, 134.7, 140.2; ESI–MS (*m*/*z*): 236 $(M+H)^+$, 258 $(M+Na)^+$; Elemental Anal. for $C_{15}H_{13}N_3$: Calcd. C 76.57, H 5.57, N 17.86; Observed: C 76.52, H 5.51; N 17.80.

3 Results and Discussion

Among the amine ligands, diamine ligands are more popular for Click reaction because they block the copper–triazolyde species from bonding with starting alkyne again and hence contribute towards increase of the yield of click reaction. We strongly believed that if copper(II) nitrate is taken as the copper source, the planarity of the nitrate counterion might also block the coordination of copper triazolyde with the starting alkyne. To test our hypothesis, an equimolar mixture of phenyl acetylene and benzyl azide was stirred with 10 mol% $Cu(NO_3)_2$ and 10 mol% diisopropylethylamine in a 1:1 EtOH–H_2O mixture for 12 h at room temperature. Ironically, no conversion was observed. We then decided to screen some monodentate and bidentate ligands such as pyridine, 3-methylpyridine, 2,6-lutidine, 4-DMAP, 2,2′-bipyridine, 1,10-phenanthroline, 8-hydroxyquinoline, 5-acetyl-2-amino-6-methyl-4-(pyridin-3-yl)-4*H*-pyran-3-carbonitrile, and 5-acetyl-2-amino-6-methyl-4-(pyridin-2-yl)-4*H*-pyran-3-carbonitrile under similar reaction conditions (Table 1). Interestingly, 5-acetyl-2-amino-6-methyl-4-(pyridin-3-yl)-4*H*-pyran-3-carbonitrile gave the highest yield (67%) in 12 h, while many other pyridine-based ligands were found to be catalytically much inferior under the reaction conditions. Increase of 5-acetyl-2-amino-6-methyl-4-(pyridin-3-yl)-4*H*-pyran-3-carbonitrile (20 mol%, entry 13–14) and reaction time (24 h, entry 14) showed only marginal increase in yield of the reaction. We carried out the same click reaction with other commonly used copper salts to see the counter ion effect on the reaction in the presence of 5-acetyl-2-amino-6-methyl-4-(pyridin-3-yl)-4*H*-pyran-3-carbonitrile. To our surprise, the commonly used counterion such as ^{-}I, Cl^-, Br^-, AcO^- and SO_4^{2-} gave inferior yields within similar reaction time under our reaction conditions (Table 1, entries 15–19).

The fact that $Cu(NO_3)_2$ is not reported in the literature and its catalytic activity in the presence of 5-acetyl-2-amino-6-methyl-4-(pyridin-3-yl)-4*H*-pyran-3-carbonitrile for the Click reaction can be termed as moderate to good under in-situ conditions, we decided to explore if the reactivity can be increased by pre-forming the copper(II) complex with 5-acetyl-2-amino-6-methyl-4-(pyridin-3-yl)-4*H*-pyran-3-carbonitrile. For that purpose, a mixture of readily accessible 5-acetyl-2-amino-6-methyl-4-(pyridin-3-yl)-4*H*-pyran-3-carbonitrile [17, 18] and $Cu(NO_3)_2{\cdot}3H_2O$ was ground in 2:1 molar ratio in a mortar with a pestle with 0.5 mmol of triethylamine at room temperature. Within 20 min, formation

Table 1 Screening of ligands and counter ion effect

Sl no.	Ligands	Cu salt	Loading (mol%)	Time (h)	% Yield[a]
1	None	$Cu(NO_3)_2$	None	12	NR
2	DIPEA	$Cu(NO_3)_2$	10	12	NR
3	Pyridine	$Cu(NO_3)_2$	10	12	37
4	3-Methyl pyridine	$Cu(NO_3)_2$	10	12	35
5	4-DMAP	$Cu(NO_3)_2$	10	12	41
6	2,6-Lutidine	$Cu(NO_3)_2$	10	12	44
7	2,2′-Bipyridine	$Cu(NO_3)_2$	10	12	24
8	1,10-Phenanthroline	$Cu(NO_3)_2$	10	12	39
9	8-Hydroxyquinoline	$Cu(NO_3)_2$	10	12	24
10		$Cu(NO_3)_2$	10	12	NR
11		$Cu(NO_3)_2$	10	12	42
12		$Cu(NO_3)_2$	10	12	67
13		$Cu(NO_3)_2$	20	12	71
14		$Cu(NO_3)_2$	20	24	73
15		CuI_2	20	24	53
16		$CuCl_2$	20	24	41
17		$CuBr_2$	20	24	47
18		$Cu(AcO)_2$	20	24	21
19		$Cu(SO_4)_2$	20	24	38

All the reactions were carried out at room temperature with EtOH–H_2O as solvent

[a]Yield of purified product

of a melt was observed which subsequently got converted to a reddish brown solid mass. TLC of the reaction mixture showed disappearance of starting 5-acetyl-2-amino-6-methyl-4-(pyridin-3-yl)-4*H*-pyran-3-carbonitrile and the formation of a highly polar compound. The reddish brown solid was heated at 60 °C for 2 h, washed with 30% ethyl acetate in petroleum ether, and dried over anhydrous $CaCl_2$ in a desiccator.

3.1 Catalyst Characterization

The structure of the copper(II) complex **1** (Fig. 1) was confirmed by IR, UV–Vis spectroscopy, Fluorescence spectroscopy, EPR spectroscopy, ESI–MS analysis, magnetic susceptibility measurements, SEM, EDAX, and elemental analyses. In spite of our repeated efforts, single crystal for the copper(II) complex **1** could not be obtained. The IR spectra of the complex showed shifting of band for C=N (aromatic) (Table S1, Supplementary materials) along with bands at 1432, 1297 cm^{-1} to indicate that nitrate group is

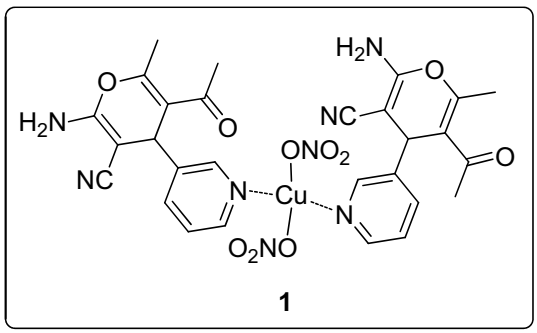


Fig. 1 Structure of the complex, **1**

bound to the metal center in monodentate fashion [19, 20]. The band occurring in the far IR region at 486 cm^{-1} is assigned to ν(Cu–N). These observations clearly pointed towards the involvement of the aromatic C=N group of 5-acetyl-2-amino-6-methyl-4-(pyridin-3-yl)-4*H*-pyran-3-carbonitrile and nitrate in complexation.

In the electronic spectra of the 5-acetyl-2-amino-6-methyl-4-(pyridin-3-yl)-4*H*-pyran-3-carbonitrile and the copper(II) complex (**1**) in a 10^{-5} M methanolic solution, the ligand showed two strong absorptions bands at 240 and 307 nm which were attributed to intraligand π–π* and n–π* transitions, respectively. On the other hand, the complex **1** showed absorption bands at 260, 301 and 359 nm due to the intraligand π–π*, π–π* and n–π* transitions, respectively. The absorption peak at 510 nm indicated d–d transition responsible for co-ordination of the ligand to the metal centre (Fig. 2) [21]. This indicated that the ligand is coordinated to the metal centre forming the copper complex.

The magnetic moment value for the copper(II) complex **1** was found to be 1.79 B.M at room temperature which is close to the magnetic moment obtained from spin only formula (1.73 B.M). This result suggested a square planner geometry of the complex and no M–M interaction in the structural unit [22].

Fluorescence studies were carried out to gather additional evidences of complexation between the ligand and the metal ion. The emission spectra of the ligand and complex were measured in the methanolic solution at room temperature. The ligand displayed a photoluminescence with emission maxima at 303 and 392 nm on excitation at 260 nm, whereas the copper(II) complex **1** showed photoluminescence with an emission maximum at 304 and 432 nm on excitation at 260 nm (Table S2, in Supplementary Materials).

The SEM image (Fig. S1, Supplementary materials) revealed the surface morphology of Cu(II) complex. The particles were agglomerated and were present as small grains of non-uniform size. Furthermore, EDX (Fig. 2S, Supporting Information) indicated that presence of Cu with energy bands of 8.01, 9.01 keV (K lines) and 0.93 keV (L line) [23]. The ESI–MS analysis of the copper(II) complex **1** gave prominent band at *m/z* 698 corresponding to $[M+H]^+$ supported the proposed structure of the complex, **1**.

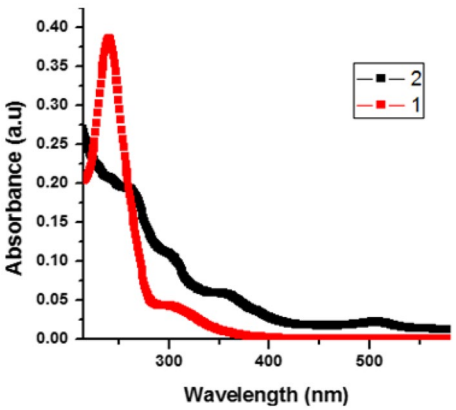


Fig. 2 UV–Vis spectra of the ligand (red) and the complex **1** (black)

The synthesized Cu(II) complex, **1** was also characterized by EPR spectroscopy, recorded for powder and solution sample at RT and LNT (Table S3, Supplementary Materials). The EPR spectra of the Cu(II) complex was anisotropic in solid state both at RT and LNT. The EPR spectrum showed hyperfine splitting in DMSO at LNT with three lines in the $g_{\parallel}$ region. The $g_{\parallel}$ and $g_{\perp}$ values for the complex **1** in polycrystalline state at RT were 2.462 and 2.115, while those at LNT were 2.501 and 2.111. The hyperfine splitting in $g_{\parallel}$ region was observed due to intermolecular interaction of unpaired electron spin of copper(II) with nuclear spin (I = 3/2). Although four hyperfine lines should be observed, only three components were visible in the $g_{\parallel}$ region which might be due to overlap of last line of split component with the strong signal in the $g_{\parallel}$ region. The observed Hamiltonian parameters are $g_{\parallel} = 2.231$, $g_{\perp} = 2.071$, $g_{av} = 2.124$, and $A_{\parallel} = 150$ G at LNT in DMSO. Although not well resolved, the LNT spectra of the complex in solution showed additional three small lines with $A_{\parallel} = 75$ G which are indicative of a pattern typical of a dimer structure involving weak Cu–Cu interaction. This observation suggests that there might be a small percentage of dimer species in solution in equilibrium with the monomeric copper(II) complex. The dimeric species might arise due to solvation of the monomeric complex in DMSO solution. The g values for the complex which are in the order of $g_{\parallel} > g_{\perp} > 2.0023$ indicated a $d_{x^2-y^2}$ ground state. The nature of the ligand forming the complex was evaluated by using the equation $[G = (g_{\parallel} - 2)/(g_{\perp} - 2)]$. The G value obtained for the complex are in the region 3.25–4.51 to suggest a moderately strong field ligand character in the complex and the local tetragonal axes are misaligned. The ratio of $g_{\parallel}/A_{\parallel}$, which is used to find the distortion in the equatorial plane of the coordination complex, was found to be 148 cm^{-1} for the copper(II) complex. This data suggested a plausible square planar geometry of the complex [24].

3.2 Catalytic Studies

The catalytic activity of the newly prepared copper(II) complex **1** was investigated for the synthesis of 1, 2, 3-triazoles employing the Click reaction. For this purpose, we carried out the reaction of benzyl azide with phenyl acetylene at room temperature with 10 mol% of the synthesized catalyst **1** in THF in the presence of sodium ascorbate as a sacrificial reducing agent. To our pleasure, the reaction led to complete conversion of the starting azide and phenyl acetylene within 30 min of vigorous stirring leading to the formation of a more polar white solid product. The product was found to be pure without further chromatographic purification with a yield of 78%. Interestingly, almost similar yield was achieved when the catalyst loading was reduced to 1 mol%. Inspired by the huge improvement in comparison

to our in-situ observations, we decided to screen the effect of solvent and catalyst loading on efficiency of the reaction (Table 2).

It was found that 1:1 mixture of ethanol and water is the optimum solvent system for the pilot reaction. A series of experiments for the pilot reaction was carried out with varying catalyst loading viz. no catalyst, 0.5, 1, 2 and 5 mol% of the complex **1**. It was found that 1 mol% of catalyst in 1:1 ethanol–water system is the optimum for the said synthesis with respect to both time and yield (entry 9, Table 2). Efficient cycloaddition was also realized with significantly lower catalyst loading although it required a longer reaction time (entry 10, Table 2).

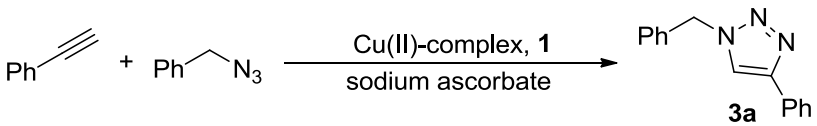
3.3 Substrate Scope

With the optimized reaction conditions in place, the substrate scope of the reaction was explored by varying both azido compounds and the terminal alkynes (Table 3). A variety of triazoles could be isolated in excellent yields and in high purity without employing any column chromatographic purification. All the benzyl azides (entries 1–3, Table 3) and secondary azides (entries 7–9, Table 3) reacted with phenyl acetylene to generate the corresponding triazoles with excellent isolated yield. It is important to note that under our optimized reaction conditions, straight chain aliphatic azide such as hexyl azide and stearyl azide (entries 10 and 11, Table 3) also yielded the corresponding triazoles in excellent yield within 20 min. In a bid to diversify the protocol, we employed different alkynes such as propargyl alcohol, 2-ethynyl pyridine and (4-pentyl phenyl)-acetylene with benzyl azide under the optimized reaction conditions to achieve the desired triazoles in excellent yields.

The fact that the click reactions have found applications in labeling of biomolecules, we tested our catalytic system for the synthesis of triazole derived from biomolecules such as cholesterol. For the purpose, we carried out the reaction of cholesterol derived azide with phenyl acetylene under our optimized reaction conditions (entry 12, Table 3). To our pleasure, in this case also we achieved the desired 1-cholesteryl 4-phenyl-1*H*-1,2,3-triazole in 93% isolated yield by simple aqueous work-up without any column chromatographic purification within 20 min. The catalytic efficiency was explored for synthesis of bis- and tris-1,2,3-triazoles (Fig. 3) and excellent results were achieved.

To establish the catalytic efficiency of our system, we selected some commonly used copper salts for click reaction that work at room temperature in the presence of various ligands (Table 4). In comparison to these methods, our method employs a readily accessible ligand, takes shorter reaction time and works at mild reaction conditions.

Table 2 Screening of solvent and catalyst loading

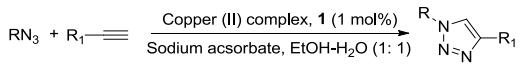


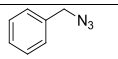
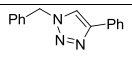
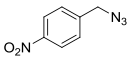
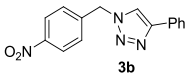
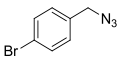
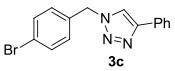
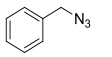
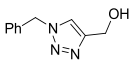
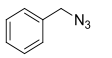
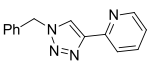
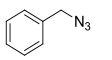
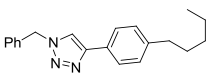
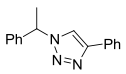
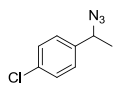
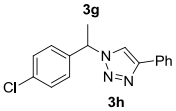
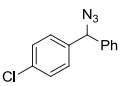
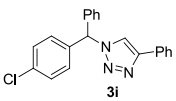
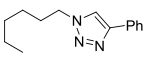
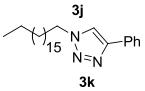
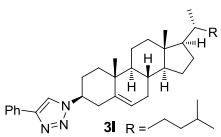
Entry	Solvent(s)	Catalyst (mol%)	Time (min)	% Yield
1	H_2O:EtOH (1:2)	1	30	88
2	H_2O:EtOH (1:1)	1	10	94
3		0.5	30	87
4		2	10	92
5		5	10	95
6	EtOH	1	45	75
7	MeOH	1	45	68
8	H_2O	1	60	72
9	THF	10	30	78
10	THF	1	30	76
11	CH_3CN	1	30	64
12	H_2O: CH_3CN (1:1)	1	40	78

Reaction condition: reaction of benzyl azide with phenyl acetylene in water at room temperature with 1 mol% of the copper(II) complex **1** in presence of sodium ascorbate

Isolated yield

Table 3 Synthesis of 1, 2, 3-triazoles



Entry	Azide	Product	t (min)	%Yield[a]
1		 **3a**	10	94
2		 **3b**	10	92
3		 **3c**	10	91
4		 **3d**	15	96
5		 **3e**	10	95
6		 **3f**	15	94
7		 **3g**	15	90
8		 **3h**	15	88
9		 **3i**	15	90
10	Hexyl azide	 **3j**	15	93
11	Stearyl azide	 **3k**	20	92
12	Cholestrol azide	 **3l** R =	20	93

Reaction conditions: reaction of azide (1 mmol) with phenyl acetylene (1 equiv.) at room temperature with the copper(II) complex **1** (1 mol%) in ethanol–water mixture (1:1) in the presence of sodium ascorbate

[a]Isolated yield

4 Conclusion

For the first time, we have established copper(II) nitrate as a catalyst for click reaction in the presence of 5-acetyl-2-amino-6-methyl-4-(pyridin-3-yl)-4*H*-pyran-3-carbonitrile, a readily available ligand synthesized from pyridine-3-carboxaldehyde, acetylacetone and malononitrile by MCR. The structure of the active catalyst was confirmed by various spectroscopic studies and its catalytic activity was evaluated for azide alkyne cycloaddition reaction under click conditions to synthesize a number of 1,4-disubstituted triazoles. Very low catalyst loading (1 mol%), short reaction time (10–20 min), room temperature reaction conditions, use of environmentally benign solvents, chromatography-free purification, readily available and cost-effective copper(II) nitrate as catalyst for click reaction are some important features of our protocol.

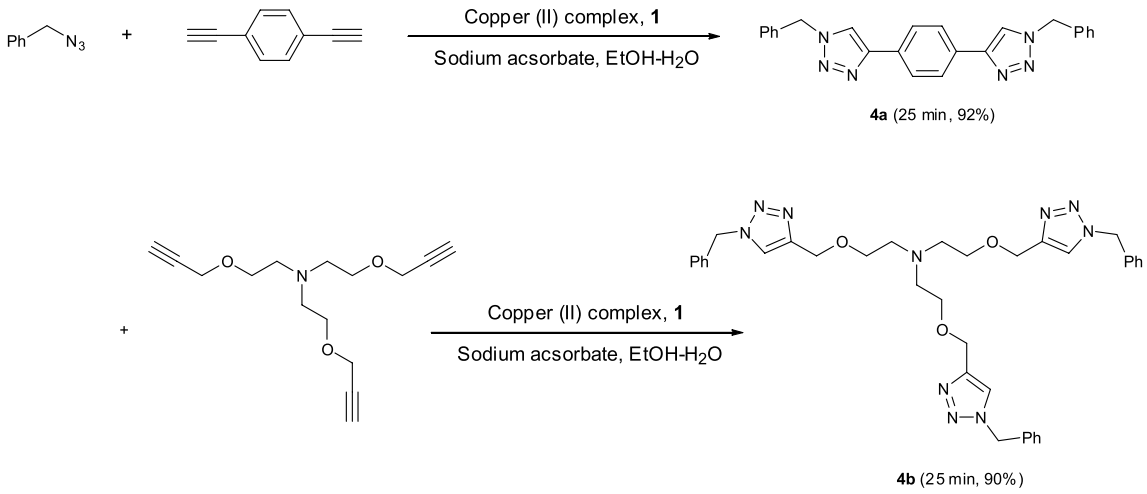
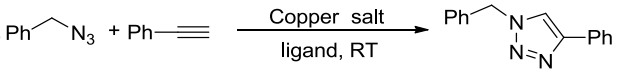


Fig. 3 Synthesis of bis- and tris-1,2,3-triazoles

Table 4 Comparative studies with reported methods



S. no.	Reaction conditions	% Yield	Ref.
1	$CuBr_2$, $Cu(CH_3CN)_4PF_6$, NaASc, *N*-((1*H*-pyrazol-3yl)methyl-1-(pyridine-2-yl) –*N*-(pyridine-2-ylmethyl))methanamine, NEt_3, N_2 atmosphere, 16 h	99	[25]
2	$CuSO_4$ in NaOH, sodium potassium tartrate, DIPEA, Hydrazine, 15 min	98	[26]
3	$CuCl_2$ or CuCl, 1,3-bis(2,6-dimethylphenyl)thiourea, 1.5 h	99	[27]
4	$CuSO_4.5H_2O$, NaASc, urea, water, 1 h	99	[28]
5	Chitosan-stabilised copper–iron oxide nanocomposite, DCM, 12 h	92	[29]
6	$CuSO_4$, (1-(4-methoxybenzyl)-1-H-1,2,3-triazol-4-yl)methanol, NaASc, PEG-H_2O, 6 h	96	[30]
7	$CuSO_4{\cdot}5H_2O$, Betaine, NaAsc, water, 30 °C, 24 h	95	[31]
8	This work, 10 min	94	

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