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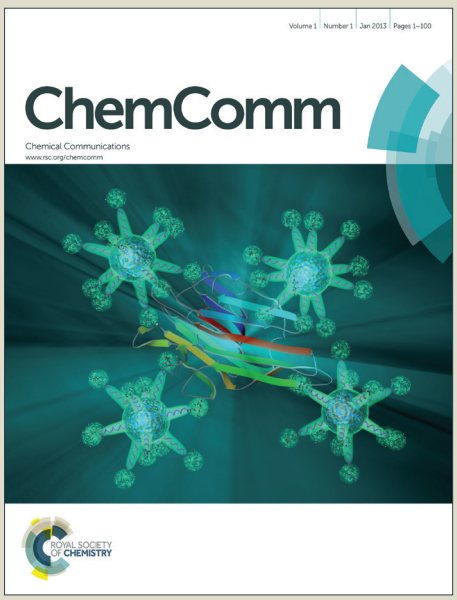

ROYAL SOCIETY OF CHEMISTRY

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Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

Nano copper catalysed highly regioselective synthesis of 2,4-disubstituted pyrroles from terminal alkynes and isocyanides

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

Nano copper(0) stabilized on alumina prepared from Cu-Al hydrotalcite has been reported for completely regioselective synthesis of 2,4-disubstituted pyrroles from unactivated terminal aromatic/ aliphatic alkynes and isocyanides. The reaction is operationally simple, involves ligand-free inexpensive nano copper, and affords high yielded products.

Oligofunctional pyrroles are an important nitrogen containing heterocyclic motif often observed in a plethora of biologically significant natural products and potent pharmaceuticals.[1] In addition, pyrrole derivatives are widely used as the building blocks in the preparation of agrochemicals, flavours, dyes, molecular sensors and other devices.[2,3] Therefore, substantial attention has been paid to develop mild and efficient methods for pyrroles synthesis and in recent past, numerous new synthetic protocols have been reported.[4] Among them, the metal catalysed [3+2] cycloaddition of isocyanides and alkynes has emerged as one of the most reliable and promising route to access substituted pyrroles due to its atom economical nature. However, the majority of reactions are reported only with activated alkynes to afford either oligo (2,3-disubstituted) or polysubstituted pyrroles.[5] Recently, Lei and Bi co-workers have reported the first transition metal catalysed regioselective synthesis of 2,3-disubstituted pyrroles by using unactivated alkynes (Figure-1, eq. 1).[6] However, the challenges for synthesizing regioselective 2,4-disubstituted pyrroles from unactivated alkynes and isocyanides remain elusive. To the best of our knowledge, only Bi group has described the silver carbonate catalysed regioselective synthesis of 2,4 disubstituted pyrroles in cycloaddition of isocyanides with 2-pyridyl alkynyl carbinols which needs to be synthesized prior to use. (Figure-1, eq. 2).[7] Therefore, the development of simple and efficient route to access 2,4-disubstituted pyrroles from easily available unactivated alkynes remains an important research objective. We have investigated an operationally simple methodology, using inexpensive copper catalyst which can catalyse the cycloaddition of isocyanides with electron deficient terminal alkynes to give regioselectively 2,4-disubstituted pyrroles.

Recently, we directed our efforts on the synthesis of mono dispersed and highly stable Cu(0) from copper aluminium hydrotalicite.[8] One of the important characteristics of nano Cu(0) on alumina (Cu_{nano}/Al_2O_3) is that it is prepared from single precursor, Cu-Al HT Brucite like structures and upon reduction, Cu (II) gets selectively reduced to Cu(0) with high dispersion and stability. Herein, we describe the regioselective route for the synthesis of 2,4-disubstituted pyrroles using isocyanides and unactivated aromatic terminal alkynes with Cu_{nano}/Al_2O_3. In addition, the catalytic activity of the Cu_{nano}/Al_2O_3 was extended to the regioselective synthesis of 2,4-disubstituted pyrroles using isocyanides with unactivated aliphatic terminal alkynes in which the substituted methylene group at C_4 undergoes oxidation to alkanoyl pyrroles (Figure-1, eq. 3).

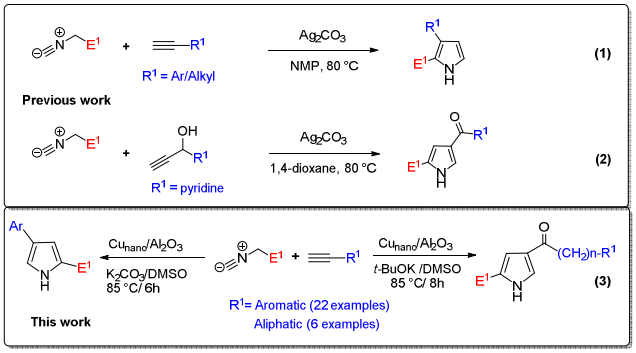


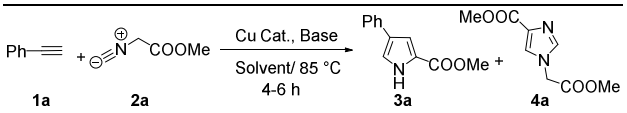
Figure 1. Scheme depicting the regioselective synthesis of 2,3- and 2,4-disubstituted pyrroles along with present study.

At the onset, the readily available phenyl acetylene (**1a**) and methyl 2-isocyanoacetate (**2a**) were selected as model substrates. Our initial efforts by treating **1a** with **2a** in the presence of freshly prepared catalyst (Cu_{nano}/Al_2O_3; 30 mg, 3.75%) in DMSO at room temperature under nitrogen atmosphere were unsuccessful (Table 1, entry 1). No improvements were observed even after changing the solvents and varying the temperatures. However, when the mixture was heated at 85 °C in the presence of base (Na_2CO_3, 1.5 equiv) under nitrogen atmosphere for 6 h, we indeed obtained 2,4-disubstituted pyrrole **3a** albeit in very low yield (5%). The major product obtained was disubstituted imidazole **4a** (90%) resulting from dimerization of methyl 2-isocyanoacetate **2a** (entry 2).[9] To our delight, a higher yield (65%) of **3a** and trace amount of imidazole **4a** were obtained when Na_2CO_3 (1.5 equiv.) was added in portions over a period of 2 h at 85 °C (entry 3). This interesting result encouraged us to continue our investigations to optimize the reaction conditions.

After several optimization efforts, the use of 3.75 mol%

catalyst (30 mg) and 1.5 equiv. of K_2CO_3 as a base in DMSO at 85 °C under nitrogen atmosphere turned out to be the best result (entry-6). A further increase in catalyst loading (7.5 mol%) resulted in lower yield (58%) of desired product **3a** (entry-5), due to dimerization of **1a**. The use of lower amount of catalyst (2.5 mol%) furnished inferior yield of **3a** along with unreacted starting material (entry-7). Furthermore, the screening of other bases such as triethylamine (Et_3N), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and potassium *tert*-butoxide (*t*-BuOK) produces the desired product in poor yields (entries 8-10).

Table 1 Optimization of the reaction conditions for aromatic alkyne.

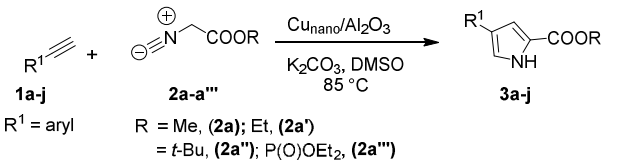


Entry	Catalyst	Base (equiv)	Solvent	*T* [°C]	Yield (%) **3a**	**4a**
1	$Cu(0)/Al_2O_3$	without base	DMSO	rt	0	0
2	$Cu(0)/Al_2O_3$	Na_2CO_3 (1.5)	DMSO	85	5	90[a]
3	$Cu(0)/Al_2O_3$	Na_2CO_3 (1.5)	DMSO	85	65	trace[b]
4	$Cu(0)/Al_2O_3$	K_2CO_3 (1.5)	DMSO	85	72	trace[b]
5	$Cu(0)/Al_2O_3$	K_2CO_3 (1.5)	DMSO	85	58	trace[c]
6	**$Cu(0)/Al_2O_3$**	**K_2CO_3 (1.5)**	**DMSO**	**85**	**75**	**trace[b]**
7	$Cu(0)/Al_2O_3$	K_2CO_3 (1.5)	DMSO	85	50	trace[d]
8	$Cu(0)/Al_2O_3$	Et_3N (1.5)	DMSO	85	42	trace[b]
9	$Cu(0)/Al_2O_3$	DBU (1.5)	DMSO	85	52	trace[b]
10	$Cu(0)/Al_2O_3$	*t*-BuOK (1.5)	DMSO	85	50	trace[b]
11	$Cu(0)/Al_2O_3$	K_2CO_3 (1.5)	DMSO	100	55	trace[b]
12	$Cu(0)/Al_2O_3$	K_2CO_3 (1.5)	DMSO	60	30	trace[b]
13	$Cu(0)/Al_2O_3$	K_2CO_3 (1.5)	CH_3CN	85	63	trace[b]
14	$Cu(0)/Al_2O_3$	K_2CO_3 (1.5)	toluene	85	41	trace[b]
15	$Cu(0)/Al_2O_3$	K_2CO_3 (1.5)	1,4-dioxane	85	43	trace[b]
16	$Cu(0)/Al_2O_3$	K_2CO_3 (1.5)	NMP	85	46	trace[b]
17	$Cu(0)/Al_2O_3$	K_2CO_3 (1.5)	DMF	85	30	trace[b]
18	$Cu(0)/Al_2O_3$	K_2CO_3 (1.5)	DCM	60	0	trace[b]
19	$Cu(0)/Al_2O_3$	K_2CO_3 (1.5)	EDC	80	0	trace[b]
20	CuI	K_2CO_3 (1.5)	DMSO	85	0	37[b]
21	$Cu(OTf)_2$	K_2CO_3 (1.5)	DMSO	85	0	41[b]
22	$Cu(OAc)_2$	K_2CO_3 (1.5)	DMSO	85	0	38[b]
23	CuCl	K_2CO_3 (1.5)	DMSO	85	0	12[b]
24	Cu_2O	K_2CO_3 (1.5)	DMSO	85	0	45[b]
25	Cu(0)/nano 60-80 nm (Aldrich)	K_2CO_3 (1.5)	DMSO	85	23	45[b]

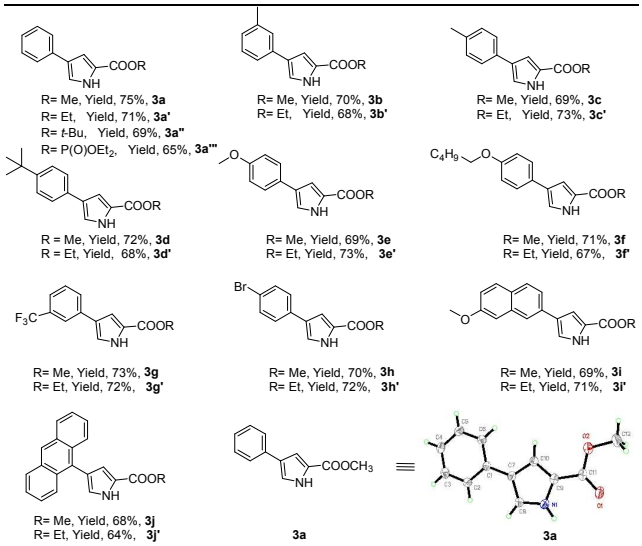
[a] Reaction was performed using **1a** (1.0 mmol), **2a** (1.0 mmol), Cat. (Cu 8 wt%, 30 mg, 3.75 mol%) and K_2CO_3 (1.5 mmol) at 85 °C for 6 h; [b] Cat. (Cu, 3.75 mol%) and gradual addition of K_2CO_3 (1.5 mmol) over a period of 2 h at 85 °C and stirred for another 4 h under nitrogen atmosphere; [c] Cat. (Cu, 60 mg, 7.5 mol%); [d] Cat. (Cu, 20 mg, 2.5 mol%). Yield indicates yields of isolated product.

The reaction temperature also noticeably influenced the product formation in this cycloaddition reaction. When the temperature was increased to 100 °C, only 55% yield of desired product could be achieved (entry 11). On the other hand, a decrease in the temperature from 85° to 60 °C afforded the desired pyrrole **3a** in 30% yield (entry 12). Next, we examined different solvents such as CH_3CN, toluene, 1,4-dioxane, NMP and DMF for this reaction but all of them produced the corresponding 2,4-disubstituted pyrrole **3a** in low yields (entries 13-17). However, no product formation was observed in chlorinated solvents such as DCM and EDC (entries 18 and 19). During our investigations, various copper salts such as CuI, $Cu(OTf)_2$, $(Cu(OAc)_2$, CuCl, Cu_2O and Cu powder (nano Cu, 60-80 nm Aldrich) were also screened, but most of them led to the formation of only undesired imidazole **4a** in (12-45%) yields, except in the case of Cu powder, which afforded 23% yield of **3a** along with **4a** in 45% yield (entries 20-25). The structure of 2,4-disubstituted pyrrole (**3a)** was well characterized using all spectroscopic techniques and confirmed by ^1H NMR, ^{13}C NMR, LR-MS, HR-MS and a single X-ray diffraction analysis.[10]

With the optimized reaction conditions, the scope of the reaction was further extended to various aromatic terminal alkynes and isocyanides. We were pleased to see that various substrates underwent the cycloaddition to afford desired 2,4-disubstituted pyrroles (**3a-a'''-3j-j'**) in moderate to good



Scheme 1[a] Scope of the Cu_{nano} catalyzed [3+2] cycloaddition reaction of aromatic alkynes (**1a-1j**) with isocyanides (**2a**-**2a'''**)



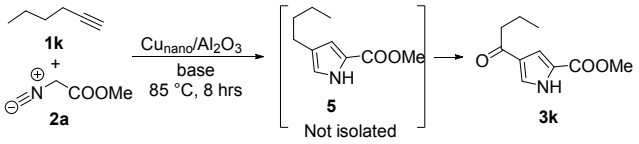
[a] Reaction was performed using **1** (1.0 mmol) with **2** (1.0 mmol) in the presence of Cu_{nano}/Al_2O_3 (Cu 8 wt%, 30 mg, 3.75 mol%) and gradual addition of K_2CO_3 (1.5 mmol) over a period of 2 h at 85 °C and stirred for another 4 h under nitrogen atmosphere. The reaction time for all the reactions is 6 h including addition of base. Yield indicates yields of isolated product.

yields (Scheme 1). Various isocyanides such as methyl 2-isocyanoacetate (**2a**), ethyl 2-isocyanoacetate (**2a'**), *tert*-butyl isocyanoacetate (**2a''**) and diethylphosphono acetonitrile (**2a'''**) were employed in the reactions and comparable yields

of corresponding products were obtained. In addition, the reaction was readily extended to a variety of aryl substituted terminal alkynes. Both electron donating and electron-withdrawing groups on the phenyl ring were found to be compatible with optimized reaction conditions (**3b-b'-3h-h'**). It is important to note that, there was no apparent steric effect on the phenyl ring since moderate to good yields of the desired products were obtained for substrate bearing groups at meta, and para positions (**3j-j' & 3b-b'-3h-h'**). The cycloaddition reaction were also performed with aromatic alkynes substituted with CF_3 (**1g**) and Br (**1h**) which resulted in good yield of the corresponding products (**3g-g' & 3h-h'**). Moreover, bicyclic and tricyclic aryl alkynes such as 6-methoxy-2-ethynylnaphthalene (**1i**) and 9-ethynyl-phenanthrene (**1j**) were also found to be suitable reacting partners and produced the corresponding substituted pyrroles **3i, 3i', 3j** and **3j'** in moderate yields.

With the above encouraging results, we focused our attention on aliphatic terminal alkynes. The reaction of hexyne-1(**1k**) with methyl 2-isocyanoacetate (**2a**) in the presence of nitrogen atmosphere afforded selectively methyl 4-butyryl-1*H*-pyrrole-2-carboxylate **3k** (12%) instead of the desired product **5** (Table 2, entry 1). The formation of **3k** was plausibly due to the aerobic oxidation of benzylic methylene group of **5** obtained from the cycloaddition of hexyne-1 (**1k**) and methyl 2-isocyanoacetate (**2a**) in the presence of copper catalyst.[11] All our efforts to isolate the intermeidate **5** were unsuccesful because it probably oxidised during work up and purifications. Therefore, we attempted the cycloaddition reaction of **1k** under air and oxygen atmosphere. Interestingly, in both the reactions, the yield of oxidized product **3k** was imrpoved to 25% and 28% respectively (entries 2, 3).

Table 2 Optimization of the reaction conditions for aliphatic alkyne **1k**.

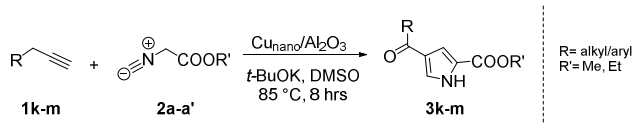


Entry	Catalyst	Base	Solvent	Yield(%)
1	Cu_{nano}/Al_2O_3	K_2CO_3	DMSO	12[a]
2	Cu_{nano}/Al_2O_3	K_2CO_3	DMSO	25[b]
3	Cu_{nano}/Al_2O_3	K_2CO_3	DMSO	28[c]
4	Cu_{nano}/Al_2O_3	Et_3N	DMSO	10[c]
5	Cu_{nano}/Al_2O_3	DBU	DMSO	7[c]
6	Cu_{nano}/Al_2O_3	Na_2CO_3	DMSO	9[c]
7	Cu_{nano}/Al_2O_3	*t*-BuOK	DMSO	46[c]
8	Cu_{nano}/Al_2O_3	*t*-BuOK	CH_3CN	11[c]
9	Cu_{nano}/Al_2O_3	*t*-BuOK	Toluene	8[c]
10	Cu_{nano}/Al_2O_3	*t*-BuOK	1,4-Dioxane	15[c]
11	Cu_{nano}/Al_2O_3	*t*-BuOK	DMF	12[c]

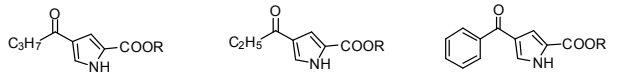
[a] Reaction was performed using **1k** (1.0 mmol), **2a** (1.0 mmol), Cat. (Cu 8 wt%, 30 mg, 3.75 mol%) and base (1.5 mmol) heated at 85 °C for 8 h; under nitrogen atmosphere; [b] under air; [c] under oxygen; Yield indicates yields of isolated product.

Further, we screened various bases such as Et_3N, DBU, Na_2CO_3 but most of them were found less effective to improve the yield (entries 4-6) except *t*-BuOK (1.5 equiv), which resulted **3k** in 46% yield (entry 7). We then screened different solvents but all of them furnished **3k** in poor yield (entries 8-11).

Next, the cycloaddition reactions of pentyne-1 (**1l**) with both methyl 2-isocyanoacetate (**2a**) and ethyl 2-isocyanoacetate (**2a'**) were performed and moderate yields of corresponding alkanoyl pyrroles (**3l, 3l'**) were obtained. On the other hand, when activated acetylene such as prop-2-yn-1-yl benzene (**1m**) was employed along with the isocyanides (**2a** & **2a'**), a better yield of **3m** and **3m'** (67% and 65%) were obtained respectively. The spectral data of alkanoyl pyrroles were in good agreement with the reported values.[12]

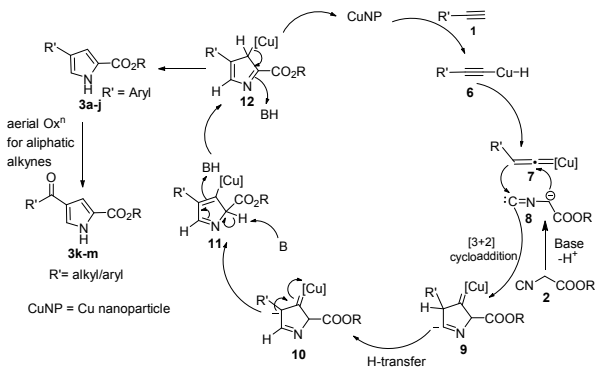


Scheme 2[a] Scope of the Cu_{nano} catalyzed [3+2] cycloaddition reaction of aliphatic acetylenes (**1k-m**) with isocyanides (**2a-a'**)



[a] Reaction was performed using **1k-m** (1.0 mmol) with **2a-a'** (1.0 mmol) in the presence of Cu_{nano}/Al_2O_3 (Cu 8wt%, 30 mg, 3.75 mol%) and *t*-BuOK (1.5 mmol) in DMSO (4 mL) at 85 °C for 8 h under O_2. Yield indicates yields of isolated product.

The plausible mechanism for the formation of 2,4 disubstituted pyrroles **3** from terminal alkynes **1** and isocyanoacetate **2** can be rationalized as depicted in Scheme 3. Phenyl acetylene gets converted into copper acetylenide **6** (*via* Cu insertion), which then rearranges to copper vinylidine intermediate **7**.[13] The deprotonation of isocyanoacetate **2** furnishes anionic species **8** which undergoes [3+2] cycloaddition with copper vinylidine **7** resulting into intermediate **9**. The latter then undergoes proton shift and rearrangement of double bond leading to **12.** The release of copper and final protonation gives the desired product (**3a**). In case of aliphatic alkynes, the benzylic methylene group undergoes air oxidation to form the alkanoyl pyrroles **3k**.[11]



Scheme 3. Plausible mechanism for the formation for pyrroles **3a-j** and **3k-m**

In summary, highly efficient regioselective [3+2] cycloaddition of aromatic alkynes with isocyanides is achieved by heterogeneous copper nanoparticles stabilised on alumina. The yield of regioselective 2,4-disubstituted pyrroles is optimized by the use of appropriate base and solvent without using external ligands. Further, the application of copper nanoparticles is extended in regioselective cycloddition of aliphatic alkynes with isocyanides to 2,4-disubstituted alkanoyl pyrroles in moderate yields. Considering, the readily availabile starting materials, broad substrate scope, operationally simple, and highly functionalized products, the present method makes an attractive option for the synthesis of the 2,4-disubstituted pyrroles. Further detailed mechanistic studies and the reusability of catalyst are currently under way in our laboratory and findings will be reported in due course.

Acknowledgement

The authors thank the Department of Science and Technology (DST) New Delhi, India, for the financial support. The authors are grateful to the Director, CSIR-IICT for providing the necessary infrastructure.

Notes and references

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† Electronic Supplementary Information (ESI) available: Datas and spectral Copies of ^{1}H, ^{13}C NMR and HRMS for target compounds. X-ray crystallograpic data of compounds **3a** See DOI: 10.1039/b000000x/

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