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# Microwave-assisted copper(I) catalyzed $A^3$ -coupling reaction: reactivity, substrate scope and the structural characterization of two coupling products

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#### ABSTRACT

The application of highly efficient catalyst [{Cu( $\mu$ -I)<sub>2</sub>Cu}(PPh<sub>3</sub>)<sub>4</sub>] for the synthesis of biologically and pharmaceutically important propargylamine derivatives through microwave assisted A<sup>3</sup>-coupling reaction is described. The A<sup>3</sup>-coupling reaction performed under microwave conditions with a catalyst loading of 0.1 mol% produced propargylamines in almost quantitative isolated yields. Most of the reactions were completed within 5 minutes. Various alkynes, amines and aldehydes were employed to produce propargylamines in excellent yields.

Keywords: Microwave; Copper(I); A<sup>3</sup>-Coupling; Catalyst; Propargylamine.

#### 1. Introduction

The coupling of an alkyne, an aldehyde and an amine to generate propargylic amines by C-H activation of terminal alkyne is popularly known as A<sup>3</sup>-coupling reaction or three components reaction (Scheme 1) [1]. Due to the enormous utility of propargylamines in the synthesis of biologically important molecules such as dibenzoazocines/dibenzoazepines [2], 1,4-diamino-2-butynes [4]. furoquinoxalines, triazolodiazepines [3]. β-lactams and oxotremorine analogues [5], one-pot A<sup>3</sup>-coupling reaction involving mild reaction conditions and cheap catalysts is a boost to the pharmaceutical and drug industries [6]. In this context,  $A^{3}$ -coupling reactions have been studied by several groups employing various metal catalysts, including calcium [7], magnesium [8], ruthenium [9], rhodium [10], iron [11], cobalt [12], nickel [13], zinc [14], iridium [15], indium [5], copper [16, 17], silver [18, 19] and gold [20] under thermal as well as microwave assisted conditions (Table 1). Further, nanoparticles of coinage metals [21, 22], solid surface support [23], ionic liquids [24] and doping [25] methodologies have also been used in these reactions. Though, A<sup>3</sup>-coupling reaction has been extensively studied, the reports on microwave assisted reactions are scarce [1-4, 26, 27]. In this paper we report A<sup>3</sup>-coupling reaction carried out under microwave condition catalyzed by simple and cheaper copper(I) catalyst,  $[{Cu(\mu-I)_2Cu}(PPh_3)_4]$  in very low concentration. The catalyst showed excellent conversion (upto 100%) within five minutes and the isolated yields of the products were also quantitative.



(R= H/alkyl/aryl/hetero atom substituted; R'= H/alkyl/aryl; R''= H/alkyl/aryl) Scheme 1. General scheme of A<sup>3</sup>-coupling reaction.

Table 1 Some reported catalysts and the A<sup>3</sup>-coupling reaction conditions

Sr.	Catalyst used	Types of	Duration of	References
No.		reaction	reaction	

1.	$[\{Rh(\mu-Cl)(H)_2(IPr)\}_2]$	Thermal	5-96 h	[10]
2.	AuBr <sub>3</sub>	Thermal	20 h	[28]
3.	$[AuI(L1)]SbF_6$	Thermal	2-6 h	[29]
4.	PANF-NHC-Ag Complex	Thermal	12 h	[30]
5.	Silver(I)-XPhos Complexes	Thermal	0.1-24 h	[19]
6.	Au-NPs	Thermal	variable time	[31]
7.	Ag-NPs	Thermal	variable time	[32]
8.	Fe-NPs	Thermal	variable time	[33]
9.	CuBr (20 mol%)	Microwave	25 min	[2, 4]
10.	CuI (30 mol%)	Microwave	30 min	[4]
11.	$GO-CuCl_2$ (20 mol%)	Microwave	20 min	[27]

#### 2. Results and discussion

Previously, several groups have reported  $A^3$ -coupling reaction using precious metals such as rhodium, gold, silver, nanoparticles (NPs) of coinage metals and as simple catalysts as copper(I) halides. Some of these catalysts and reaction conditions are listed in Table 1. Most of these reactions have been carried out under thermal conditions with temperature ranging from 60-100 °C over a period of 12-96 h or using microwave radiations over a period of 20-30 min. In the present investigation, copper(I) complex, [{Cu( $\mu$ -I)<sub>2</sub>Cu}(PPh<sub>3</sub>)<sub>4</sub>] works well with aromatic as well as aliphatic alkynes, aldehyde (paraformaldehyde) and secondary amines. Variables such as solvents, temperature, catalysts and catalyst loading were optimized by carrying out A<sup>3</sup>-coupling reaction under microwave power of 80 W as shown in Scheme 1.

Initially, the reaction of phenylacetylene, *para*-formaldehyde and N-ethylbenzylamine in 1:1.1:1 molar ratio was performed in acetonitrile at 85 °C for 30 min using 5 mol% CuX (X = Cl, Br and I) as catalyst did not show any conversion which may be due to the less reactivity of CuX aggregates which remain intact in the absence of Lewis bases (Table 2,

CuI: entry 1, CuBr: entry 2, CuCI: entry 3) [26]. The same reaction when carried out using 5 mol% catalyst [{Cu( $\mu$ -I)<sub>2</sub>Cu}(PPh<sub>3</sub>)<sub>4</sub>] in toluene at 110 °C for 30 min showed 50% conversion (Table 2, entry 4), whereas in water at 100 °C and in acetonitrile at 85 °C, the conversions were 70% (Table 2, entry 5) and 100% (Table 2, entry 6), respectively. Under similar reaction condition, 0.1 mol% catalyst also showed the same result (Table 2, entry 7). However on further decreasing the catalyst loading to 0.01 mol% only 40% conversion (Table 2, entry 8) was observed. Reaction performed under the above condition without any catalyst showed no conversion (Table 2, entry 9). The same reaction carried out under conventional thermal condition showed about 57% conversion within 1 h and it took nearly 6 h for the complete conversion (Table 2 entry 10). Thus, based on the above trials, the best optimized conditions for A<sup>3</sup>-coupling reaction depicted in entry 7 was adopted (i.e. 0.1 mol% [{Cu( $\mu$ -I)<sub>2</sub>Cu}(PPh<sub>3</sub>)<sub>4</sub>], time: 5 min. and temperature: 85 °C).

Entry	Catalyst	Solvent	Temp.	Time	Conv.	Yield
			°C		(%)	(%)
1	CuI	CH <sub>3</sub> CN	85	30 min	00	00
2	CuBr	CH <sub>3</sub> CN	85	30 min	00	00
3	CuCl	CH <sub>3</sub> CN	85	30 min	00	00
4	$[{Cu(\mu-I)_2Cu}(PPh_3)_4]$	Toluene	110	30 min	50	50
5	$[{Cu(\mu-I)_2Cu}(PPh_3)_4]$	$H_2O$	100	30 min	70	70
6	$[{Cu(\mu-I)_2Cu}(PPh_3)_4]$	CH <sub>3</sub> CN	85	30 min	100	100
$7^{d}$	$[{Cu(\mu-I)_2Cu}(PPh_3)_4]$	CH <sub>3</sub> CN	85	5 min	100	100
8 <sup>e</sup>	$[{Cu(\mu-I)_2Cu}(PPh_3)_4]$	CH <sub>3</sub> CN	85	5 min	40	40
9	No catalyst	CH <sub>3</sub> CN	85	30 min	00	00
$10^{\mathrm{f}}$	$[{Cu(\mu-I)_2Cu}(PPh_3)_4]$	CH <sub>3</sub> CN	85	6 h	100	

Table 2 Optimization of coupling reaction conditions<sup>a</sup>

<sup>a</sup>Reaction conditions: alkyne (1 equivalent), paraformaldehyde (1.1 equivalent), 2<sup>o</sup> amines (1 equivalent), catalyst (5 mol %), solvents (2 mL); in a microwave vessel (10 mL) power (80 W); <sup>b</sup>Conversion was determined by GC and GC-MS. <sup>c</sup>Isolated yields after column

chromatography, <sup>d</sup>Catalyst loading upto 0.1 mol%, <sup>e</sup>Catalyst loading upto 0.01 mol%. <sup>f</sup>Reaction was performed under thermal condition

In order to investigate the generality of the optimized reaction conditions, different types of substrates such as secondary amines (N-ethylbenzylamine, morpholine, diisopropylamine, piperazine, N-methylpiperazine, diphenylamine) with different types of substituted acetylenes trimethylsilylacetylene (ethynyltrimethylsilane)) (phenylacetylene, 1-Pentyne and were reacted with aldehyde (Table 3, Entry 1-19); excellent conversions were observed with very good isolated yields of the products (Table 3). The substrate scope is wide for amines and alkynes but in the case of aldehydes no product was formed with benzaldehyde (Table 3, Entry 12). However, on increasing the catalyst loading from 0.1 to 10 mol%, reaction of PhC=CH, PhCHO and N-ethyl, benzyl amine showed 22% conversion, whereas the same reaction with morpholine and diethylamine showed quantitative conversions (Table 3, entry 12). In order to examine the durability of the catalyst, the same catalyst was used in five successive catalytic cycles and no change in the catalytic efficiency was observed. Only in the  $6^{th}$  and  $7^{th}$  the cycles, the conversions were reduced by only 5-7%.

The overall conversion was in the range of 72-100% with good isolated yields and all the products have been characterized by <sup>1</sup>H NMR, <sup>13</sup>C{<sup>1</sup>H} NMR, mass spectrometry and molecular structures of two of the products have been confirmed by single crystal X-ray analysis.

**Table 3**  $A^3$ -coupling reaction of terminal alkynes with secondary amines and aldehydes (para-formaldehyde and benzaldehyde)<sup>a</sup>

Entry	Alkyne	Amine	Product	Code	Con.	Yield <sup>b</sup>
					%	(%)

1	C <sub>6</sub> H <sub>5</sub> −C≡CH	HN C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub> −C≡C N CH <sub>3</sub>	A <sup>3</sup> -1	100	97
2	C <sub>6</sub> H <sub>5</sub> —C≡CH	HNO	$C_6H_5$ $C_6H_5-C\equiv C$	A <sup>3</sup> -2	100	95
3	C <sub>6</sub> H <sub>5</sub> —C≡CH	⊥ H	C <sub>6</sub> H <sub>5</sub> −C≡C N−	A <sup>3</sup> -3	100	98
4	C <sub>6</sub> H₅—C≡CH	Н		A <sup>3</sup> -4	100	96
5 <sup>d</sup>	C <sub>6</sub> H₅—C≡CH			A <sup>3</sup> -5	100	99
6	C <sub>6</sub> H₅−C≡CH	HN_N-CH <sub>3</sub>		A <sup>3</sup> -6	100	97
7	C <sub>6</sub> H <sub>5</sub> —C≡CH	HN <sup>∠C</sup> 6H₅	$C_6H_5 - C \equiv C - N - C_6H_5$	A <sup>3</sup> -7	100	92
8	CH₃(CH₂)₂C≡CH		$C_6\dot{H}_5$ CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> C $\equiv$ C $N$	A <sup>3</sup> -8	100	98
9 <sup>d,f</sup>	CH <sub>3</sub> (CH <sub>2</sub> )₂C≡CH		$\begin{array}{c} & CH_{3} \\ & C_{6}H_{5} \\ H_{3}C(H_{2}C)_{2} \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ $	A <sup>3</sup> -9	100	98
10	CH₃(CH₂)₂C≡CH		$H_3C(H_2C)_2-C\equiv C$	A <sup>3</sup> -10	100	96
11	CH <sub>3</sub> (CH <sub>2</sub> )₂C≡CH	HN_N-CH <sub>3</sub>		A <sup>3</sup> -11	100	91
	R	HN C <sub>6</sub> H <sub>5</sub>	$C_6H_5$ $C_6H_5$ $C_6H_3$	A <sup>3</sup> -12	22	-
12 °	C <sub>6</sub> H <sub>5</sub> −C≡CH ≺	HNO	$C_6H_5$ $C_6H_5$ $C_6H_5$	A <sup>3</sup> - 12A	100	-
		- HN	$C_6H_5$	A <sup>3</sup> - 12B	100	-



[a] optimized conditions; [b] Isolated yields of product; [c]  $C_6H_5CHO$  (1.1 equiv), conversions are based on GCMS; [d] alkyne, formaldehyde and piperazine, in 1:1.1:0.5 molar ratio; [f] new compounds.

### 2.1 Possible catalytic cycle for A<sup>3</sup>-coupling reaction

The catalytic cycle (Fig. 1) shows a plausible mechanism for  $A^3$ -coupling reaction. Firstly an amine and an aldehyde form imine by condensation, and alkyne and copper(I) form an alkenylcopper complex. The mixture of these two compounds is termed as **A**. Intermediate **A** shows concerted mechanism of nucleophilic alkyne attack on activated imine carbon to form a C–C bond resulting in the intermediate **B**. Finally decomplexation results in the formation of propargylamine (**C**) and the regeneration of copper(I) catalyst as suggested by Van der Eycken [1].



**Fig. 1.** Proposed catalytic cycle for microwave assisted  $[{Cu(\mu-I)_2Cu}(PPh_3)_4]$  catalyzed A<sup>3</sup>-coupling reaction.

### 2.2 Molecular structures of $A^3$ -5 and $A^3$ -13 (deprotected)

The molecular structures of products  $A^3$ -5 and  $A^3$ -13 (deprotected) are confirmed by single crystal X-ray analyses. The slow diffusion of petroleum ether into the saturated solution of  $A^3$ -5 and  $A^3$ -13 (deprotected) in ethyl acetate yielded colourless crystals suitable for single crystal X-ray analysis. The centrosymmetrically substituted piperazine compound adopts chair conformation and both the acetylene and the substituted acetylene arms are *trans* to each other. The average N-C bond distances of CH<sub>2</sub>–N in both the structures are 1.463(2) Å. The average N-C-C bond angle in piperazine and acetylene molecules is 114.62(14)°. The bond length and bond angles are shown in Fig. 2.



Fig. 2. Solid state molecular structure of  $A^3$ -5 and  $A^3$ -13 (deprotected). All hydrogen atoms and solvent molecule have been omitted for clarity. Thermal ellipsoids are drawn at the 50%

probability level. Selected bond distances (Å) and bond angles (deg): ( $A^3$ -5): N1–C9 = 1.462(2) N1–C11 = 1.472(2), N1–C10 = 1.467(2), C7–C8 = 1.203(2), C8–C9 = 1.485(2), C9–N1–C11 = 111.78(13), C9–N1–C10 = 111.82(13), C10–N1–C11 = 109.78(13), C7–C8–C9 = 175.77(17).  $A^3$ -13 (deprotected): N1–C5 = 1.466(2), N1–C4 = 1.465(2), N1–C3 = 1.464(2), C1–C2 = 1.190(3), C2–C3 = 1.483(3), C4–N1–C5 = 109.59(15), C3–N1–C5 = 111.85(14), C3–N1–C4 = 112.31(15), C1–C2–C3 = 177.49(19).

#### 3. Experimental section

#### 3.1 General Procedure for A<sup>3</sup>-Coupling Reaction

The reactions were performed in a closed vessel containing a mixture of alkyne (1 equivalent), amine (1.0 equivalent), (CH<sub>2</sub>O)<sub>n</sub> (1.1 equivalent), and catalyst (0.1 mol %) in acetonitrile (2 mL). The microwave irradiation power of 80 W was applied to reach a temperature of 85 °C. After a specified reaction time, the reaction mixture was filtered and dried under reduced pressure. The residue was diluted with H<sub>2</sub>O (8 mL) and Et<sub>2</sub>O (8 mL), and twice extracted with Et<sub>2</sub>O (6 mL) and the combined organic fractions were dried over MgSO<sub>4</sub> or Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed under reduced pressure. The crude products were purified by column chromatography using petroleum ether/ethyl acetate mixture as eluent. Yields were calculated against alkyne.

#### 3.2 X-ray crystallography

A crystal of each of the compounds in the present work suitable for single crystal X-ray diffraction studies was mounted in a Cryoloop with a drop of Paratone oil and placed in the cold nitrogen stream of the kryoflex attachment of the Rigaku Saturn 724+ (4×4 bin mode) diffractometer (See Supporting Information). Data were collected at different temperatures (Table S1), using graphite-monochromated MoK $\alpha$  radiation ( $\lambda \alpha = 0.71073$  Å) using the  $\omega$ -scan technique. The data were reduced by using Crystal Clear- SMExpert 2.1 b24 software. Crystal data and summary of data collection for compounds are given in crystallographic data (Table S1). The structures  $A^3$ -5 and  $A^3$ -13 (deprotected) were solved by direct methods and

refined by least-squares against F2 utilizing the software packages SHELXL-97/2013 [34]. All non-hydrogen atoms were refined anisotropically. Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1560999 (compound  $A^3$ -5), 1561000 (compound  $A^3$ -13- deprotected).

#### 4. Conclusions

In Summary, we have developed a simple and efficient method for  $A^3$ -coupling or three component reaction using copper(I) complex, [{Cu( $\mu$ -I)<sub>2</sub>Cu}(PPh<sub>3</sub>)<sub>4</sub>] under microwave irradiation conditions. The utility of cheap triphenylphosphine-copper complex and its easy synthetic method and low catalyst loading (0.1 mol%) has broadened the scope of  $A^3$ coupling reactions. Despite low catalyst loading, the same catalyst remained efficient even after 5 cycles and only in the 6 and 7<sup>th</sup> cycles the catalytic efficiency was reduced by a margin of 6-7%. Further, this method works smoothly for both aromatic and aliphatic alkynes, and both cyclic and acyclic secondary amines. Five novel products have been isolated and some of them can serve as valuable synthons for the synthesis of new types of ligands and click-products with rich coordination chemistry. Further studies into applications of this methodology is in progress.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at

https://www.journals.elsevier.com/catalysis-communications

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### **Graphical abstract**

Microwave-assisted copper(I) catalyzed A<sup>3</sup>-coupling reaction: reactivity, substrate scope and the structural characterization of two coupling products



 $A^3$ -coupling reaction of an alkyne, aldehyde and amine carried out under microwave condition (85  $^oC$  and 80 W) catalyzed by 0.1 mol% [{Cu(\mu-I)\_2Cu}(PPh\_3)\_4] in 5 min. is described.

### **Research highlights**

- Simple and easy to prepare catalyst:  $[{Cu(\mu-I)_2Cu}(PPh_3)_4]$
- Low cost and a very low catalyst loading (0.1 mol%)
- Lesser reaction time (5 minutes) as compare to traditional thermal conditions
- Scope for substrates of various alkynes and secondary amines
- Excellent conversion and isolated yields of all products

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