Current Chemistry Letters 1 (2012) 69–80

Contents lists available at Growing Science

Current Chemistry Letters

homepage: www.GrowingScience.com/ccl

Conventional and microwave-assisted multicomponent reaction of alkyne, halide and sodium azide catalyzed by copper apatite as heterogeneous base and catalyst in water

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ARTICLE INFO

Article history:
Received February 08, 2012
Received in Revised form
Feb 19, 2011
Accepted 10 March 2011
Available online
11 March 2012

Keywords:
Multicomponent reaction
Solid base catalyst
Water
Green solvent
Microwave

ABSTRACT

The conventional and microwave assisted multicomponent synthesis of disubstituted 1,2,3-triazoles from terminal alkynes and in situ generated organic azide using copper apatite catalyst in water is reported. The catalytic activity is intimately connected to the basicity of the catalyst. The best activities were observed with the copper hydroxyapatite. The catalyst could be used ten times without further treatment and activation under controlled microwave heating. The protocol was also applicable for various alkynes and halides which affords desired product in good to excellent yield.

1. Introduction

Multicomponent reactions[1] are the important class of organic synthesis that involves transformation of various reactants into the desire product in a single step. The development of novel, heterogeneous and recyclable catalysts for the multicomponent reaction in water[2] as green, environmentally acceptable solvent promoted by MW irradiation is of much interest and relevance.

Heterogeneous catalysis in synthesis of various organic moieties has attracted the attention of organic chemists because of their synthetic utility[3], easy isolation of product, recovery and reusability of the catalyst. The multicomponent reaction of alkynes and azides formed in situ from alkyl halides

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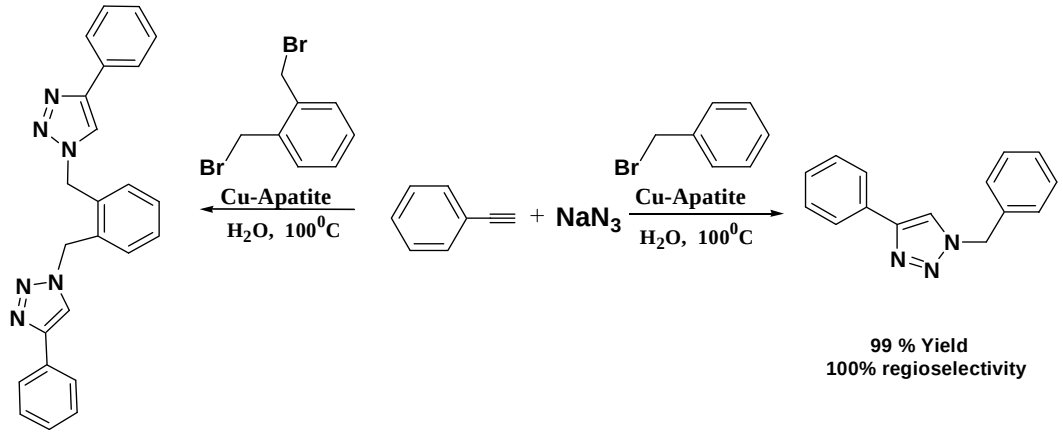
doi: 10.5267/j.ccl.2012.3.002

and sodium azide yielding 1,2,3-triazoles is a powerful one pot three component click reaction. Triazoles are the important class of compounds with wide range of biological activity such as anti-allergical[4], anti-infective agent[5], anti-HIV activity[6], and anti-bacterial[7].

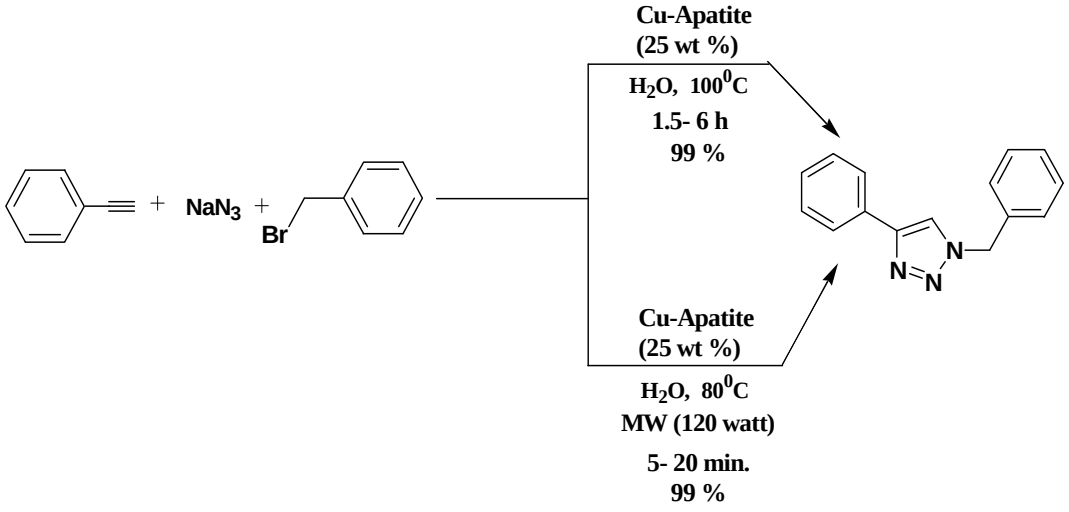
The copper-mediated cycloaddition of alkynes and insitu formed azides appears to be a method of choice, but it is often limited by the need to employ harsh reaction conditions. A variety of organic solvents has been reported for this cycloaddition reaction including toluene[8], dioxane[9], benzene[10], CH_2Cl_2[11], acetonitrile[12], DMSO[13], THF[14], H_2O[15]. Organic azides are potentially explosive, hazardous and care should be taken while handling such chemicals.

We herein report a rapid and green approach to achieve 1,4-disubstituted triazoles via three component reactions of alkynes and in situ generated azides in the presence of copper apaptite as a heterogeneous and recyclable catalyst in aqueous media. To the best of our knowledge this is the first report for the synthesis of triazoles using microwave in the presence of copper apatite in water. More importantly, the method does not require the addition of a base (scheme 1).



Scheme 1

Recently, Sharghi et. al. had reported the use of copper nanoparticle supported on carbon for the cycloaddition of alkynes and in situ formed organic azides in water[16]. Namitharan et. al. reported for the first time Cu^{II} an active species in the cycloaddition of terminal alkynes and azides in a non aqueous solvent.[17] Rivero I. A. et al. reported conventional and microwave assisted synthesis of triazoles using Cu(I) salt.[18] Kaneda et. al. exploit catalytic application of hydroxyapatite as a solid support on Pd to perform organic transformations[19] that includes Oxidation of alcohols and Heck reaction. Kantam et. al. utilized copper apatite as a heterogeneous and recyclable catalyst for coupling of phenyl acetylene, amine and aromatic aldehydes to afford propargalylamines.[20]



Scheme 2.

2. Results and Discussions

To develop a suitable protocol for the cycloaddition reaction, the reaction of phenyl acetylene (1mmol), sodium azide (1.2 mmol) and benzyl bromide (1mmol) in the presence of copper apatite (25 wt %) using water was chosen as a model reaction (scheme 2). Surprisingly no base was needed for the copper apatite catalyzed cycloaddition of alkynes and in situ formed azides. The catalyst itself acts as base and removes the acetylenic proton to form copper acetylide species.

To probe the active species involved in the reaction, we carried out the reaction of diphenyl acetylene with benzyl bromide and sodium azide but reaction did not take place which might indicates that there should be interaction of catalyst with terminal alkynes to form copper acetylide species. The influence of different catalysts, catalyst loading and reaction temperature were tested for cycloaddition reaction and found that the reaction does not take place in the absence of copper containing catalyst (Table 1. Entry 1-2). By using these results we studied the activity different copper containg catalyst and revealed that copper hydroxyapatite (Cu-HAP) is found to be efficient catalyst for the cycloaddition reaction promoted by controlled microwave irradiation.

Table 1. Optimization of different reaction parameter [a]

		Conventional				Microwave			
Entry	Catalyst	Catalyst	Time	Temp.	Yield[b]	MW	Time	Temp.	Yield[b]
Effect of Catalyst									
1	Co-HAP	25	48	100	0	120	30	80	0
2	Zn-HAP	25	48	100	0	120	30	80	0
3	Cu-HAP	25	1.5	100	99	120	5	80	99
4	Cu-FAP	25	1.5	100	85	120	5	80	83
5	Cu-CAP	25	1.5	100	81	120	5	80	79
6	Cu/Cr-HT	25	1.5	100	61	120	5	80	56
7	Cu/Al-HT	25	1.5	100	72	120	5	80	65
Effect of Catalyst Loading									
8	Cu-HAP	0	1.5	100	0	120	5	80	0
9	Cu-HAP	10	1.5	100	56	120	5	80	48
10	Cu-HAP	20	1.5	100	82	120	5	80	81
11	Cu-HAP	25	1.5	100	99	120	5	80	99
12	Cu-HAP	30	1.5	100	99	120	5	80	99
Effect of Temperature									
13	Cu-HAP	25	1.5	30	13	60	5	60	42
14	Cu-HAP	25	1.5	50	68	120	10	60	78
15	Cu-HAP	25	1.5	70	80	120	5	80	99
16	Cu-HAP	25	1.5	85	86	120	10	80	99
17	Cu-HAP	25	1.5	100	99	120	5	100	99
18	Cu-HAP	25	1.5	120	99	120	10	100	99

[a] Reactions were performed with phenyl acetylene (1 mmol), benzyl halide (1 mmol) and sodium azide (1.2 mmol), catalyst (25 wt %) in 3 mL water, [b] GC Yield. HAP-Hydroxyapatite, FAP-fluroapatite, CAP-Chloroapatite, HT-Hydrotalcite

We investigated the activity of the catalyst with respect to time for the formation of triazole (Table 3, Entry 1 product) and found the 1.5 h and 5 min. is the optimized reaction time at 100^0C for conventional and microwave methods respectively. An increase in the catalyst loading from 10 wt % (1 mol % of Cu) to 25 wt % (2.7 mol % of Cu) resulted in an increase in the yield up to 99%. Further

increase in catalyst loading had no profound effect on the yield of the desired product. Also the reaction was carried out at different temperature ranging from room temperature (30^0C) to 120^0C and found that at 100^0C the yield of the reaction was 99% in 1.5 h by conventional method and at 80^0C it was found to be 99% in 5 min by microwave method. Further increase in the temperature, does not affect the yield of the reaction.

For comparison copper fluroapatite (Cu-FAP) and copper chloroapatite (Cu-CAP) were prepared by coprecipitation method using NH_4F and NH_4Cl respectively and studied their catalytic activity for cycloaddition reaction. The catalytic activity of the Cu-HAP is higher than Cu-FAP and Cu-CAP, it may be due to the highest surface area and basicity of the catalyst as shown in table 2. We also compare the activity of the copper hydroxyapatite catalyst with the copper containing hydrotalcite and found that Cu/Cr hydrotalcite (Cu/Cr-HT) and Cu/Al hydrotalcite has low basicity and hence gives low yield of the desired product. Therefore it can be conclude that higher the basicity, higher will be the reactivity irrespective of total surface area (Table 2).

Table 2. Study of physico chemical properties

Catalyst	Surface area (m^2g^{-1})	Basicity (mmol g^{-1})	Initial rates (mmol h^{-1} g^{-1}) X 10^3
Cu-HAP	179	0.149	2.291
Cu-FAP	159	0.144	1.843
Cu-CAP	173	0.137	1.840
Cu/Cr-HT	235	0.0494	1.183
Cu/Al-HT	201	0.0344	1.598

Initial rate are calculated with respect to product (table 3, entry 1). The basicity of the catalyst was measured by phenol adsorption method. The amount of phenol adsorb by the catalysts was determined using following formula,

$$q_e = \frac{(Co-Ce)\ X\ V}{W}$$

where, q_e – quantity of phenol adsorb,
Co- initial conc. of phenol,
Ce- conc. of phenol at equilibrium,
W- wt. of the catalyst (gm).

In order to make our catalytic system greener and economical, we focused on reusability of catalyst on multicomponent reaction of phenyl acetylene, sodium azide and benzyl bromide as shown in figure 1. It is important to note that the catalyst was successfully reused ten times in aqueous medium without separation, further purification and activation. The catalyst was recycled ten times without any significant loss of activity as shown in Fig 1. Based on ICP-AES analysis, copper content in catalyst was found to be 0.6154 mmol/g. After reaction, the copper content in catalysts was found 0.6148 mmol/g, revealed that copper apatite catalyzed cycloaddition of alkynes and in situ formed azide takes place heterogeneously with a negligible leaching of copper species during recyclability experiment. We carried out standard leaching experiment as earlier reported in literature.[21] It was found that the reaction preceded heterogeneously and no homogeneous catalyst was involved while performing the reaction. Encouraged by these results, we explored the scope of the cycloaddition reaction of different alkynes with various aromatic and aliphatic halides under same reaction conditions in aqueous medium. The results are summarized in Table 3.

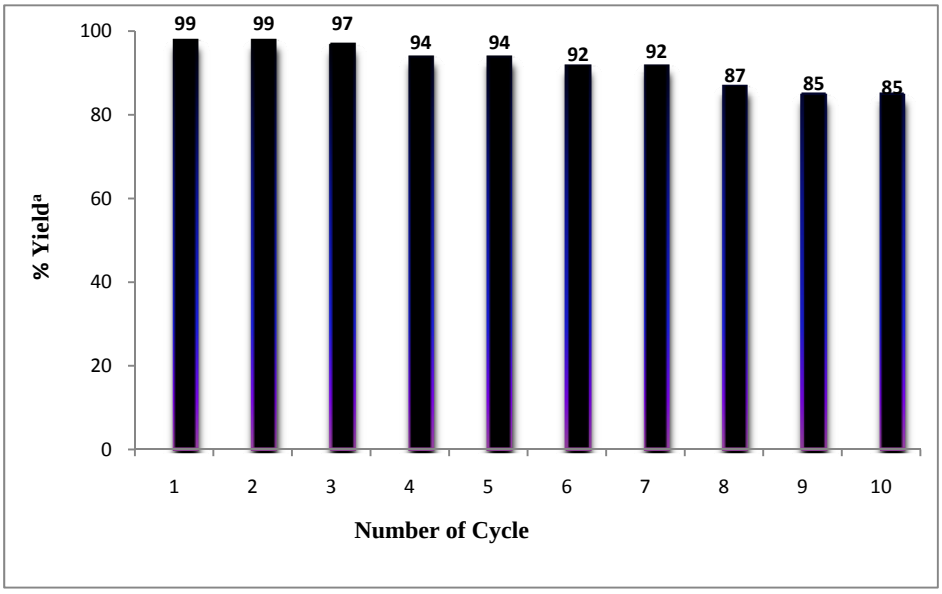
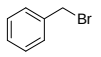
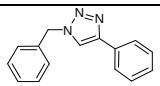
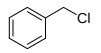
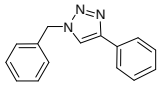
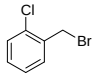
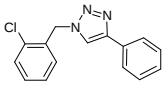
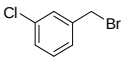
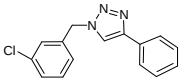
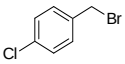
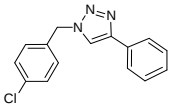
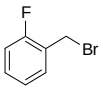
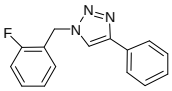
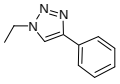
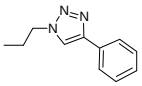
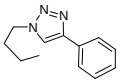
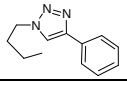
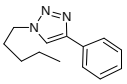
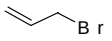
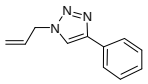
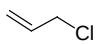
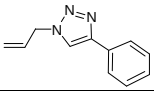
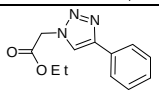
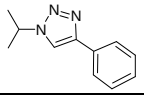


Fig. 1. Reusability of the catalyst

Aliphatic halides containing more than six carbon atoms give very low yields of triazole products, which can be attributed to a steric effect. The aromatic as well as primary and secondary aliphatic halides also give moderate to good yield of the corresponding triazole derivatives (Table 3, Entry 7-15).

Table 3. Substrate scope

			Conventional[a]		Microwave[d]	
Entry	Halides	Triazoles[b]	Time (h)	Yield[c] (%)	Time (min)	Yield[c] (%)
Alkyne: Phenyl acetylene						
1			1.5	99	5	99
2			1.5	98	5	97
3			2	90	7	88
4			2	92	7	90
5			2	93	7	91
6			2	96	7	95
7			4	92	15	91
8			6	89	15	87
9	C_4H_9Br		5	87	15	88
10	C_4H_9I		5	88	15	90

11	$C_5H_{11}Cl$		5	87	15	89
12			3	87	15	89
13			3	85	15	88
14			1.5	95	10	96
15			6	90	15	91
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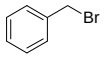
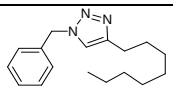
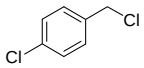
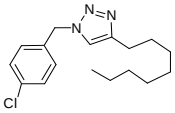
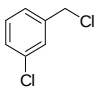
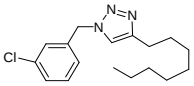
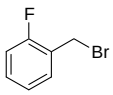
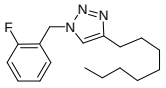
16			4	90	10	89
17			4	85	10	86
18			4	88	10	83
19			4	91	10	92
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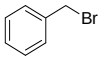
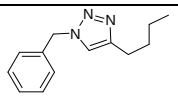
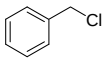
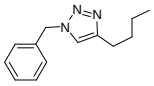
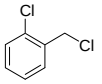
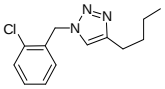
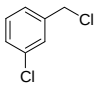
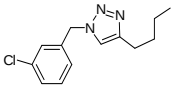
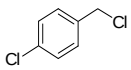
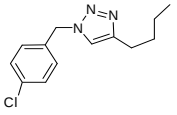
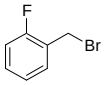
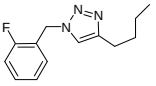
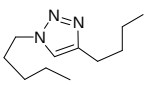
20			3	92	8	92
21			3	89	8	90
22			5	87	10	82
23			4	90	10	86
24			4	91	10	85
25			3	93	10	91
26	$C_5H_{11}Cl$		6	90	20	88
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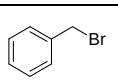
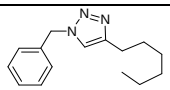
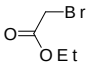
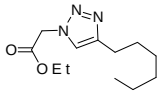
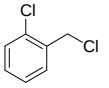
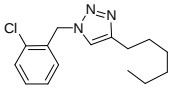
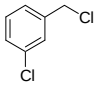
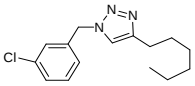
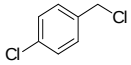
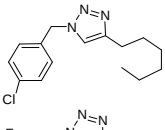
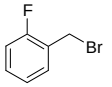
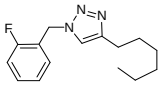
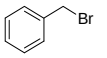
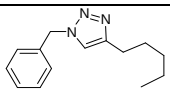
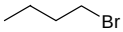
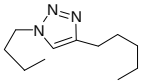
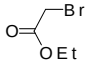
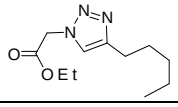
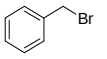
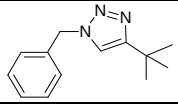
27			4	91	20	89
28			3	92	8	91
29			3	90	10	91
30			3	92	10	94
31			3	89	10	91
32			2.5	93	10	94
Alkyne: 1-heptyne						
33			4	94	7	94
34			4.5	89	20	92
35			3	92	10	95
Alkyne: t-butyl acetylene						
36			7	73	20	81

[a] Reactions were performed with alkyne (1 mmol), halide (1 mmol) and sodium azide (1.2 mmol) in 3 mL water, 25 wt % of catalyst w.r.t. halide, 100^0C. [b] All the prepared compound were confirmed by IR, ^{1}HNMR, ^{13}CNMR and GC-MS. [c] GC Yield. [d] Microwave heating perform on 120 watt power and 80 ^{0}C.

3. Conclusion

In this work a efficient methodology for rapid and green synthesis of 1,2,3 triazoles with excellent yield via multicomponent reaction in aqueous media promoted by controlled microwave irradiation and conventional heating is developed. Microwave irradiation dramatically reduces the time and temperature, which is an important factor on the viability of new organic transformations. The protocol was also applicable for various alkynes and halides, which affords desired product in good yield under microwave heating. The catalyst could be reused in the same reaction medium. Further studies aimed at broadening the panel of application of this highly stable, active, inexpensive, heterogeneous and easily prepared copper apatite catalyst are in progress.

Experimental Section

General

NMR spectra were recorded on a Varian Mercury Plus NMR spectrometer (^{1}H NMR at 300 MHz and ^{13}C NMR at 75 MHz) in pure deuterated solvents. IR spectra were recorded using a Perkin Elmer FT-IR spectrum 100 spectrophotometer. Mass spectra were determined using on a Shimadzu GCMS QP 2010 instrument. GC of all compounds was determined on Thermo Scientific GC [capillary column, 30 m × 60 mm, ID-BP1 0.25 UM] Melting points were determined in capillary using digital melting point apparatus. Elemental analysis was done on Harieus rapid analyser. The reactions were

monitored by TLC. Column chromatography of some compounds was carried out using silica gel having 60-120 mesh size. The chemicals required were purchased from S.D.Fine and Sigma Aldrich and were used as received. Wide angle XRD patterns of the catalyst were obtained on a Rigaku, Japan, miniflex X-ray Diffractometer with monochromatic Cu-Kα beam (λ =0.154 nm). The diffractometer was operated at 30KV and 15mA using a scanning step of 2 in two theta and a dwell time of 1 second was used. Microwave irradiation was carried out in a microwave single-mode reactor (Biotage, Initiator).

GC method

GC (capillary column, 30 m × 60 mm, ID-BP1 0.25 UM.): oven rate (10^0C ·min^{-1}), initial column temp. (353 K), final column temp. (523 K), injection temperature (533 K), detection temperature (543 K), halt (2 min.).

Preparation of the Copper hydroxyapatite

A solution of $Ca(NO_3)_2{\cdot}4H_2O$ (94.4g, 0.4 mol) and $(NH_4)_2HPO_4$ (31.68 g, 0.24 mol) was prepared by dissolving corresponding salts in 600 ml and 1000 ml distilled water respectively. Both the solutions were added in a round bottom flask with constant stirring. The pH of the solution was maintained to 11-12 by drop-wise addition NH_4OH. The solution was vigorously stirred at room temperature and the obtained milky solution was heated at 90^0C for about 10-15 min. The resultant slurry was then filtered, washed with distilled water and dried overnight at 110^0C, giving $Ca_{10}(PO_4)_6(OH)_2$ (HAP). 2 g of HAP was stirred in aqueous solution of copper acetate (0.800 g, 4 mmol) at 60^0C yielding copper apatite (Cu content: 0.6154 mmol/g). The catalyst was characterized using various techniques such as XRD, FT-IR, ICP-AES, DSC-TGA, and SEM analysis.

General procedure for the formation of triazoles under thermal condition

In a 10 ml round bottom flask fitted with a magnetic stirrer, the catalyst (25 wt % w.r.t halide, 2.7 mol % of Cu), alkynes (1 mmol), sodium azide (1.2 mmol) and halides (1 mmol) were stirred in water (3 ml) at 100^0C, for 1.5 h. The reaction progress was monitored by TLC. After 1.5 h, the product was extracted with chloroform. The obtaining organic layer was washed with water and dried over sodium sulfate. The chloroform solvent was removed using rotary evaporator, which left 99 % pure desired product (0.232 g). The aqueous layer containing catalyst was reused for further run without removing catalyst from the flask. All the prepared compounds were confirmed by GC-MS, IR, ^{1}H and ^{13}C NMR.

General procedure for the formation of triazoles under microwave condition

In a 5 ml microwave reactor vessel, the catalyst (25 wt % w.r.t halide, 2.7 mol % of Cu), alkynes (1 mmol), sodium azide (1.2 mmol) and halides (1 mmol) were added in water (3 ml). The resultant mixture was heated under microwave at 80^0C, for 5 min. and then cooled to room temperature. After 5 min, the product was extracted with chloroform. The obtaining organic layer was washed with water and dried over sodium sulfate. The chloroform solvent was removed using rotary evaporator, which left desired product (0.232 g, 99 %). The aqueous layer containing catalyst was reused for further run without removing catalyst from the flask.

Recycling of the catalyst

For practical application of heterogeneous system, the stability of the catalyst and its reusability are the most important factor. For that reaction of phenyl acetylene, benzyl bromide and sodium azide was chosen to test the catalyst reusability. The reaction was performed at 80^0C for 5 min. After reaction completed, chloroform was added in to reaction mixture. The organic layer was separated using a pipette without disturbing aqueous layer and catalysts. After separating the product, fresh aliquots of alkynes (1mmol), halides (1 mmol) and sodium azide (1.2 mmol) were added in to same reaction flask for the next cycle of the reaction.

Spectral data

1-Benzyl-4-phenyl-1*H*-1.2.3-triazole (Table 3, Entry 1): Retention time (17.85 min); White solid, mp 126-128^{o}C; **IR** (KBr): 694, 729, 768, 1049, 1076, 1223, 1358, 1466, 3121 cm-1; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.23(2H, s, CH_2), 7.26-7.41(6H, m, Ar), 7.69(1H, s, CH), 7.79-7.82(4H, m, Ar); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 54.1, 119.7, 125.7, 128, 128.2, 128.7, 128.8, 129.1, 130.6, 134.7, 148.1; **MS**: m/z (%): 235 (20), 207 (12), 206 (52), 180 (9), 179(7), 116 (100), 91 (98), 65 (30), 77 (5), 51 (10); **Elemental analysis**: found C 75.62, H 5.48, N 18.12, Calcd for C 75.59, H 5.53, N 17.87

1-(2-chlorobenzyl-4-phenyl-1*H*-1.2.3-triazole (Table 3, Entry 3): Retention time (19.17 min); White solid, mp 90-92 ^{o}C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.67 (2H, s, N-CH_2), 7.16-7.46 (7H, m, 3H of Ar & 4H of Ar-Cl), 7.78 (1H, s, CH of triazole ring), 7.80-7.83 (2H, d, Ar); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 51.36, 119.91, 125.64, 127.56, 128.14, 128.76, 129.83, 130.13, 130.15, 130.40, 132.49, 133.31, 147.99; **MS**: m/z (%): 269 (12), 240 (10), 206 (50), 207(5), 179 (5), 138 (9), 116 (100), 89 (48), 63 (18), 77 (5), 51(5).

1-(3-chlorobenzyl-4-phenyl-1*H*-1.2.3-triazole (Table 3, Entry 4): Retention time (19.44 min); White solid, mp 106-108^{o}C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.54 (2H, s, N-CH_2), 7.16-7.43 (7H, m, 3H of Ar & 4H of Ar-Cl), 7.69 (1H, s, CH of triazole ring), 7.79-7.82 (2H, d, Ar); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 53.4, 119.72, 125.68, 128.05, 128.01, 128.28, 128.85, 128.91, 130.33, 130.43, 134.92, 136.67, 148.31; **MS**: m/z (%): 269 (12), 240 (20), 206 (12), 207(5), 179 (5), 138 (9), 116 (100), 89 (35), 63 (18), 77 (5), 51(5).

1-(4-chlorobenzyl-4-phenyl-1*H*-1.2.3-triazole (Table 3, Entry 5): Retention time (19.14 min); White solid, mp 140-142^{o}C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.52(2H, s, CH_2), 7.17 (2H, d, J =8.4 Hz, Ar), 7.24-7.44 (5H, m, Ar), 7.67 (1H, s, CH), 7.80 (2H, d, J =8.4 Hz, Ar); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 53.4, 119.7, 125.6, 128.2, 128.8, 129.31, 129.35, 130.37, 133.24, 134.76, 148.32; **MS**: m/z (%): 269 (8), 240 (16), 206 (12), 179 (7), 138 (8), 125 (38) 116 (100), 89 (32), 63 (15), 77 (5), 51(5).

1-(2-Florobenzyl-4-phenyl-1*H*-1.2.3-triazole (Table 3, Entry 6): Retention time (17.46 min); White solid, mp 102-104^{o}C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.62 (2H, s, N-CH_2), 7.09-7.42 (7H, m, Ar), 7.76-7.82 (2H, m, Ar); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 47.67, 115.63, 115.90, 119.75, 121.88, 122.07, 124.83, 125.66, 128.71, 130.46, 130.81, 130.91, 148.14, 158.82, 162.11; **MS: m/z** (%): 253 (20), 224 (32), 198 (10), 130 (7), 124 (20), 116 (100), 109 (68), 102 (5), 89 (26), 83 (18), 77 (5), 63 (12), 51(5).

1-ethyl-4-phenyl-1*H*-1.2.3-triazole (Table 3, Entry 7): Retention time (12.14 min); White solid, mp 54-56^{o}C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 1.57 (3H, triplet, J =7.33 Hz, CH_3), 4.45 (2H, quartet, J =7.33 Hz, N-CH_2), 7.76 (1H, s, N-CH), 7.26-7.38 (3H, m, Ar), 7.80-7.83 (2H, d, ortho to Ar); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 15.50, 15.57, 45.23, 45.34, 119.02, 125.65, 128.06, 128.81, 129.78, 130.69, 147.74; **MS**: m/z (%): 173 (35), 144 (25), 130 (68), 117 (100) 103 (22), 90 (70), 89 (60), 77 (10), 63 (26), 51(15).

1-propyl-4-phenyl-1*H*-1.2.3-triazole (Table 3, Entry 8): Retention time (12.86 min); White solid, mp 62-64^{o}C, **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 0.85-0.98 (3H, t, CH_3), 1.88-1.98 (2H, m, CH_2- CH_3), 4.30-4.35 (2H, t, N-CH_2-CH_2- CH_3), 7.26-7.43 (3H, m, Ar), 7.81-7.84 (2H, d, Ar), 7.75 (1H, s, CH); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 23.72, 29.68, 51.92, 119.52, 125.62, 128.01, 128.78, 130.70, 147.61; **MS**: m/z (%): 187 (25), 144 (13), 131 (35), 117 (100), 103 (26), 90 (35), 77 (15), 41(25).

1-butyl-4-phenyl-1*H*-1.2.3-triazole (Table 3, Entry 9): Retention time (14.24 min); White solid, mp 48-50^{o}C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 0.96 (3H, t, J =7.33 Hz, CH_3-CH_2), 1.38 (2H, sextet, J =7.33 Hz, CH_2-CH_2- CH_3), 1.92 (2H, quintet, J =7.33 Hz, CH_2-CH_2- CH_2), 4.39 (2H, t, J =7.33 Hz, N-CH_2), 7.26-7.44 (3H, m, Ar), 7.74 (1H, s, N-CH), 7.82 (2H, d, Ar); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 13.57, 19.78, 32.37, 50.19, 119.48, 125.73, 128.12, 128.88, 130.79, 147.76; **MS**: m/z (%): 201 (24),

172 (18), 145 (14), 144 (12), 130 (17), 117 (100), 90 (24), 89 (22), 77 (12), 41 (25); **Elemental analysis**: found C 71.56, H 7.39, N 20.68, Calcd for C 71.64, H 7.46, N 20.89

1-pentyl-4-phenyl-1*H*-1.2.3-triazole (Table 3, Entry 11): Retention time (13.14 min); White solid, mp 68-70^{o}C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 0.91 (3H, triplet, CH_3), 1.32-1.41 (4H, m, CH_2-CH_2), 1.95 (2H, quintet, *J* =7.33 Hz, CH_2), 4.39 (2H, triplet, *J* =7.33 Hz, N-CH_2), 7.32-7.45 (3H, m, ortho to Ar), 7.74 (1H, s, N-CH), 7.82-7.85 (2H, d, *J* =8.4 Hz, Ar); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 13.83, 22.07, 28.55, 30.01, 50.37, 119.35, 125.62, 128.012, 128.77, 130.69, 147.65; **MS**: m/z (%): 215 (25), 186 (20), 172 (9), 158 (5), 145(1), 144(15), 130 (17), 117 (100), 104(25), 89 (24), 77 (14), 63 (10), 41 (50); **Elemental analysis**: found C 71.58, H 7.54, N 19.97, Calcd for C 71.55, H 7.90, N 19.53

1-allyl-4-phenyl-1*H*-1.2.3-triazole (Table 3, Entry 12): Retention time (13.20 min); White solid, mp 58-60^{o}C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 4.96-4.99 (2H, d, *J* =6.2 Hz, N-CH_2), 5.27-5.36 (2H, dd, *J* =8 Hz & 16.86 Hz, allylic CH_2), 6.01-6.09 (1H, m, allylic CH), 7.27-7.43 (3H, m, Ar), 7.76 (1H, s, CH of triazole ring), 7.80-7.83 (2H, d, Ar); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 51.36, 119.91, 120.08, 125.63, 128.08, 128.77, 130.54, 131.26, 147.88; **MS**: m/z (%): 185 (20), 156 (18), 116 (100), 89 (30), 63 (15), 77 (5), 41(16).

(4-Phenyl-1,2,3-triazole-1-yl)-acetic acid ethyl ester (Table 3, Entry 14): Retention time (15.64 min); White solid, mp 102-104^{o}C; **IR** (KBr): 768, 1045, 1078, 1223, 1466, 1758, 2950, 3004, 3079, 3125 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 1.33 (3H, triplet, *J* =7.69 Hz), 4.26 (2H, quartet, *J* =7.69 Hz), 5.20 (2H, s, N-CH_2), 7.40-7.41 (3H, m), 7.83-7.86 (2H, m, ortho to Ar), 7.91 (1H, s, CH); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 14.05, 51.01, 62.39, 121.08, 125.74, 128.21, 128.80, 130.32, 148.12, 166.28; **MS**: m/z (%): 231 (30), 203 (14), 160 (18), 146 (20), 131 (40), 130 (50), 116 (100), 103 (62), 77 (42), 51 (18); **Elemental analysis**: found C 61.80, H 5.39, N 17.49, Calcd for C 61.63 H 5.62 N 17.58

1-isopropyl-4-phenyl-1*H*-1.2.3-triazole (Table 3, Entry 15): Retention time (15.92 min); Light Yellow solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 1.59 (6H, d, *J* =8.4 Hz, 2 CH_3), 4.85 (1H, m, *J* =8.4 Hz, N-$CHMe_2$), 7.26-7.43 (3H, m, Ar), 7.77 (1H, s, N-CH), 7.82 (2H, d, ortho to Ar); **^{13}C NMR** (75MHz, $CDCl_3$) δ: 23.08, 23.14, 53.02, 53.17, 117.18, 125.71, 128.06, 128.85, 130.90, 147.54; **MS**: m/z (%): 187 (30), 159 (10), 144 (50), 132 (5), 117 (100), 103 (20), 102 (10), 89 (38), 77 (5), 63 (16), 51 (10), 43 (25), 41 (20).

1-benzyl-4-butyl-1*H*-1.2.3-triazole (Table 3, Entry 20): Retention time (15.72 min); White solid, mp 56-58^{o}C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 0.90 (3H, triplet, *J* =7.69 Hz, CH_3), 1.25-1.39 (2H, sextet, *J* =7.69 Hz, CH_2), 1.60 (2H, quintet, *J* =7.69 Hz, CH_2), 2.68 (2H, triplet, *J* =7.69 Hz, CH_2), 5.48 (2H, singlet, N-CH_2), 7.19-7.39 (6H, m, Ar); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 13.78, 22.29, 25.36, 31.48, 53.92, 120.44, 120.55, 127.92, 128.54, 129.01, 134.99, 148.89; **MS**: m/z (%): 215 (2), 173 (7), 144 (5), 130 (4), 104 (6), 91 (100), 69 (4), 65 (12), 41(10).

1-(2-chlorobenzyl)-4-butyl-1*H*-1.2.3-triazole (Table 3, Entry 21): Retention time (17.12 min); White solid, mp 90-92^{o}C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.52(2H, s, CH_2), 7.17 (2H, d, *J* =8.4 Hz, Ar), 7.24-7.44 (5H, m, Ar), 7.67 (1H, s, CH), 7.80 (2H, d, *J* =8.4 Hz, Ar); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 53.4, 119.7, 125.6, 128.2, 128.8, 129.31, 129.35, 130.37, 133.24, 134.76, 148.32; **MS**: m/z (%): 249 (2), 214 (2), 207 (7), 186 (4), 144 (4), 127 (32), 125 (100), 96 (3), 89 (21), 69 (6), 41 (15).

1-(3-chlorobenzyl)-4-butyl-1*H*-1.2.3-triazole (Table 3, Entry 22): Retention time (16.62 min); Light yellow solid, mp 50-52^{o}C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 0.98 (3H, triplet, *J* =7.69 Hz), 1.35 (2H, sextet, *J* =7.69 Hz), 1.63 (2H, quintet, *J* =7.69 Hz), 2.69 (2H, triplet, *J* =7.69 Hz), 5.46 (2H, singlet, N-CH_2), 7.20-7.33 (5H, m); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 13.74, 22.23, 25.29, 31.38, 53.12, 120.67, 120.57, 125.87, 128.68, 130.26, 134.78, 136.96, 149.03; **MS**: m/z (%): 249 (1), 220 (2), 207 (10), 178 (3), 164 (2), 138 (4), 127 (31), 125 (100), 89 (20), 69 (8), 41 (18).

1-(4-chlorobenzyl)-4-butyl-1*H*-1.2.3-triazole (Table 3, Entry 23): Retention time (20.97 min); White solid, mp 54-56^{o}C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 0.91 (3H, triplet, *J* =7.69 Hz), 1.38 (2H, sextet, *J* =7.69 Hz), 1.63 (2H, quintet, *J* =7.69 Hz), 2.63 (2H, triplet, *J* =7.69 Hz), 5.46 (2H, singlet, N-CH_2), 7.17-7.39 (5H, m); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 13.84, 22.37, 25.43, 31.53, 53.27, 120.54, 129.31, 133.58, 134.68, 149.20; **MS**: m/z (%): 249 (1), 207 (8), 178 (2), 164 (1), 138 (4), 127 (30), 125 (100), 89 (18), 69 (3), 41 (15).

1-(2-fluorobenzyl)-4-butyl-1H-1.2.3-triazole (Table 3, Entry 25): Retention time (17.10 min); Brown oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 0.91 (3H, triplet, *J* =7.69 Hz), 1.37 (2H, sextet, *J* =7.69 Hz), 1.62 (2H, quintet, *J* =7.69 Hz), 2.69 (2H, triplet, *J* =7.69 Hz), 5.45 (2H, singlet, N-CH_2), 7.10-7.39 (5H, m); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 13.76, 22.25, 25.29, 31.43, 47.40, 115.79, 120.74, 122.29, 124.72, 130.59, 148.85, 158.76, 162.05; **MS**: m/z (%): 233 (1), 204 (2), 191 (8), 176 (2), 162 (6), 122 (5), 109 (100), 96 (6), 83 (12), 69 (5), 41(11).

1-pentyl-4-butyl-1H-1.2.3-triazole (Table 3, Entry 26): Retention time (12.49 min); Yellow oil; **^{1}H NM**R (300 MHz, $CDCl_3$) δ: 0.87-0.95 (6H, m, $2CH_3$), 1.29-1.44 (6H, m, $3CH_2$), 1.65 (2H, quintet, *J* =7.33 Hz, CH_2), 1.86 (2H, quintet, *J* =7.33 Hz, CH_2), 2.71 (2H, triplet, *J* =7.33 Hz, CH_2), 4.30 (2H, triplet, *J* =7.33 Hz, N-CH_2), 7.27 (1H, s, N-CH); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 13.91, 22.16, 22.37, 25.42, 28.67, 29.74, 30.11, 31.66, 50.21, 120.44, 148.45; **MS**: m/z (%): 195 (9), 151 (4), 152 (16), 124 (20), 110 (25), 96 (26), 82 (40), 68 (26), 54 (70), 41 (100).

Acknowledgement

S.R. Kale thankful to the Council of Scientific and Industrial Research, New Delhi for financial support in the form of CSIR-JRF fellowship.

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