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Magnetically separable $CuFe_2O_4$ nano particles catalyzed multicomponent synthesis of 1,4-disubstituted 1,2,3-triazoles in tap water using 'click chemistry'

B. S. P. Anil Kumar, K. Harsha Vardhan Reddy, B. Madhav, K. Ramesh, Y. V. D. Nageswar *

Natural Product Chemistry, Indian Institute of Chemical Technology, Hyderabad 500607, India

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ABSTRACT

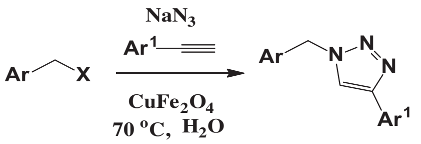
The synthesis of 1,4-disubstituted 1,2,3-triazoles is attempted using magnetically separable and reusable copper ferrite nano particles in a one pot reaction, in tap water.

Green chemistry relates to the design of a process that minimizes the use and generation of hazardous substances. Green catalysis is one of the key areas of green chemistry. The use of benign solvents (e.g., water, ionic liquids) as well as efficient and cleanly reusable catalytic materials is significant in the practice of green chemistry. Nano catalysts enjoy several advantages over the conventional catalyst systems. Although, a significant enhancement of catalytic activity can be achieved by synthesizing a catalyst in nanometer dimensions, recovery of these tiny nano catalysts from the reaction mixture is not easy and most of the heterogeneous systems require a filtration or centrifugation step and/or a tedious work-up of the final reaction mixture to recover the catalyst. Conventional techniques (such as filtration) are not efficient because of the nano size of the catalyst particles. This limitation hampers the economics and sustainability of these nano catalytic protocols. To overcome the separation problems of the nano catalysts, magnetically active nano particles have recently emerged as viable alternatives to conventional materials for catalyst supports.[1]

Magnetic separation is an attractive alternative to filtration or centrifugation as it prevents loss of the catalyst and increases reusability. Their insoluble and paramagnetic nature enables easy and efficient separation of the catalysts from the reaction mixture with an external magnet. The paramagnetic character, results in remarkable catalyst recovery, without the need for filtration step. This makes the catalyst cost-effective and promising for industrial applications.[2] The use of magnetic nano particles has been studied extensively for various biological applications such as magnetic resonance imaging, drug delivery, and bio molecular sensors.[3]

On the other hand, the catalysis of organic reactions in aqueous medium has received much attention in recent years, since the studies on Diels alder reactions by Breslow.[4] Water is a preferred solvent medium compared to the other organic solvents because water is the most abundant, safe, nontoxic, inexpensive, and environ-friendly solvent.

1,2,3-Triazoles have attracted interest over the past few years as their moieties have been widely used in pharmaceuticals, agro chemicals, dyes, photographic materials, corrosion inhibition[5] etc. 1,2,3-Triazoles are also associated with a wide range of biological properties such as antiviral, antiepileptic, antiallergic,[6] anticancer,[7] anti HIV,[8] and antimicrobial activities against gram positive bacteria.[9] In general, these compounds are prepared through the coupling reaction between alkynes and azides at high temperatures,[10] and by using solid supports.[11] Sharpless et al. used Cu (I) salts to promote the reaction of azide with terminal alkynes to afford 1,4-disubstituted products.[12] Fokin and co-workers have developed the reaction under microwave conditions. In the micro-



Scheme 1.

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* Corresponding author. Tel.: +91 40 27191654; fax: +91 40 27160512. *E-mail address:* dryvdnageswar@gmail.com (Y.V.D. Nageswar).

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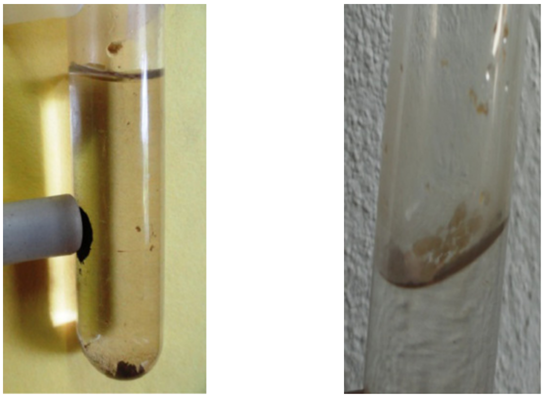


(a) (b)

Figure 1. (a) Magnetic separation of $CuFe_2O_4$ nano particles and (b) product floating on water after the reaction.

wave assisted synthesis, reaction time gets drastically reduced to 15–20 min, the temperature being raised to 125 °C.[13] Moreover in recent years, several methods have been reported for the synthesis of triazoles.[14]

Most of the literature methods involve azides, as starting materials, as well as organic solvents as reaction media. Although, these organic azides are stable against most reaction conditions, low molecular weight azides are explosive and difficult to handle.[15] A few procedures have been reported that involve the generation of azides in situ followed by the addition of alkyne as well as azide cycloaddition.[16] Recently, Francisco Alonso reported a method using copper on activated carbon, for the synthesis of 1,2,3-triazoles. It involves the in situ generation of azides by using sodium azide in the presence of alkynes.[17] However, most of the above methods suffer from drawbacks such as the use of organic solvents, use of metal catalysts with solid supports as well as difficult experimental procedures to separate the catalyst. In view of the above shortcomings, there is a need to broaden the scope of one pot multi

Table 1

Synthesis of triazoles using $CuFe_2O_4$ nano particles in water[a]

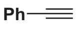
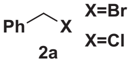
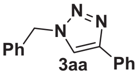
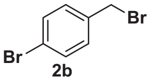
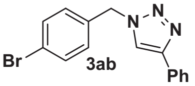
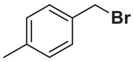
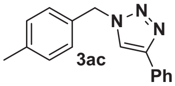
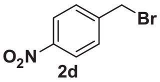
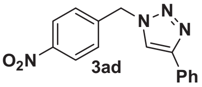
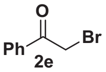
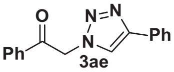
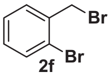
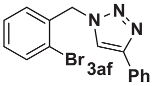
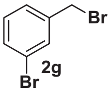
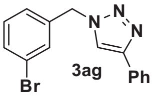
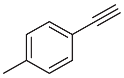
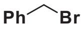
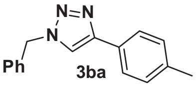
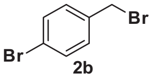
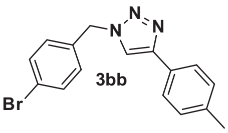
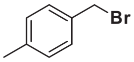
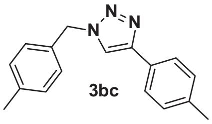
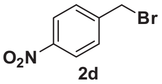
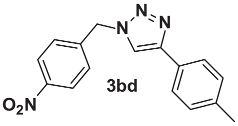
Entry	Alkyne 1	Organic halide 2	Triazole 3	*t* (h)	Yield[b] (%)
1	 **1a**	 **2a**	 **3aa**	3 6	93 80
2	1a	 **2b**	 **3ab**	4	86
3	1a	 **2c**	 **3ac**	4	85
4	1a	 **2d**	 **3ad**	5	86
5	1a	 **2e**	 **3ae**	8	78
6	1a	 **2f**	 **3af**	4	83
7	1a	 **2g**	 **3ag**	4	82
8	 **1b**	 **2a**	 **3ba**	4	83
9	1b	 **2b**	 **3bb**	4	84
10	1b	 **2c**	 **3bc**	4	84
11	1b	 **2d**	 **3bd**	5	80

Table 1 (*continued*)

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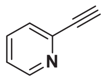
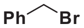
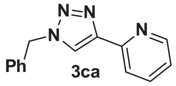
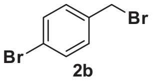
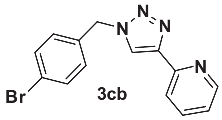
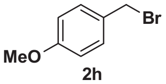
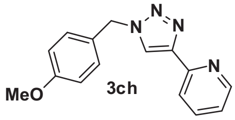
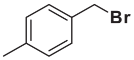
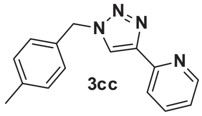
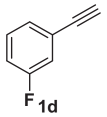
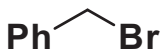
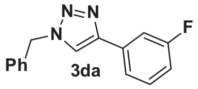
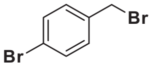
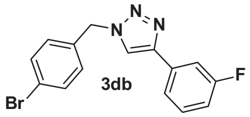
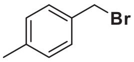
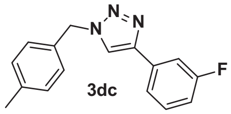
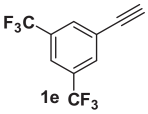
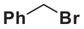
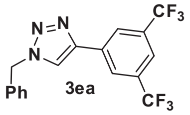
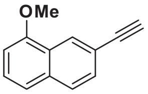
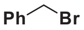
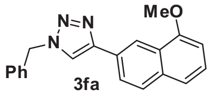
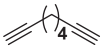
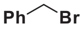
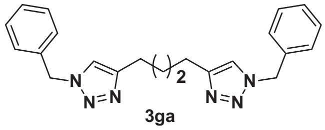
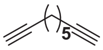
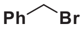
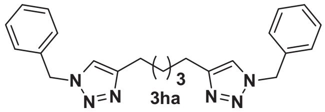
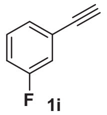
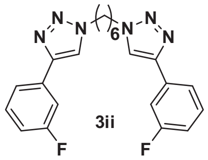
12	 1c	 2a	 3ca	4	86
13	1c	 2b	 3cb	4	82
14	1c	 2h	 3ch	5	79
15	1c	 2c	 3cc	4	83
16	 1d	 2a	 3da	4	85
17	1d	 2b	 3db	4	84
18	1d	 2c	 3dc	4	82
19	 1e	 2a	 3ea	6	83
20	 1f	 2a	 3fa	7	82
21	 1g	 2a	 3ga	9	74
22	 1h	 2a	 3ha	9	75
23	 1i	 2i	 3ii	9	76

[a] Reaction conditions: Alkyne (1 mmol), organic halide (1 mmol), NaN_3 (1.1 mmol), $CuFe_2O_4$ (12 mg) in H_2O (2 mL) at 70 °C.

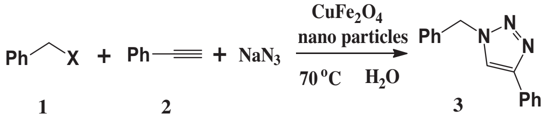
[b] Isolated yield.

step reactions, in combination with 'click reaction', without using a solid support.[18]

As a part of our continuous research in the field of aqueous medium organic synthesis[19] and copper nano catalysts,[20] we investigated the reaction by using magnetically separable nano copper ferrite as a catalyst and without using any solid support. Because of the magnetic property of the catalyst, we can easily separate it from the reaction mixture and reuse it without any loss. Moreover, the catalyst is also commercially available. The reaction proceeds via a three-component reaction between various benzyl bromides, phenyl acetylenes, and sodium azide in water.

The present methodology (Scheme 1) involves the in situ preparation of the organic azide and also reduces the number of steps as well as the time involved in the reaction strategy.

Table 2
Recyclability of nano-$CuFe_2O_4$ catalyst[a]



Cycle	Isolated product yield (%)	Catalyst recovery (%)
Native	93	92
1	90	89
2	88	85
3	84	82

[a] Reaction conditions: Benzyl bromide (1 mmol), phenyl acetylene (1 mmol), NaN_3 (72 mg, 1.1 mmol) and $CuFe_2O_4$ (5 mol %, 12 mg) in H_2O (2 mL) at 70 °C and 3 h.

The advantages of the present protocol are short reaction pathway and the use of aqueous medium at moderate temperatures for the conduct of the reaction. It also reduces and minimizes the hazards derived from the isolation and handling of the azides. This one pot procedure[21] exhibits higher atom-economy, deliver fewer by-products compared to the classical stepwise synthetic routes. The synthetic utility of this protocol is further made more attractive, as the reactions are carried out in tap water, with magnetically separable nano copper ferrite as catalyst.

In the initial studies, we selected the reaction between benzylbromide, sodium azide, and phenyl acetylene in the presence of copper ferrite nano catalyst in water at 70 °C and as expected, the cyclo addition reaction proceeded well. The azide was generated in situ from the nucleophilic substitution reaction of organic halide with sodium azide. The azide generated in situ in this reaction reacted with the terminal alkyne to give 1,4-disubstituted 1,2,3-triazole. The progress of the reaction is monitored by TLC. Most importantly, the product phase separated out from the aqueous medium after completion of the reaction, which in turn enabled the isolation of the final product by simple decantation (Fig. 1). Furthermore, there is no need for column chromatography to separate the products from the reaction mixture except in the bistriazole products (entries 21–23). By comparing the ^1H NMR data, with the literature reports, the product was confirmed as 1,4-disubstituted 1,2,3-triazole but not as 1,5-disubstituted 1,2,3-triazole.[17,22] On completion of the reaction, the catalyst was magnetically separated from the reaction mixture, using an external magnet. The separated catalyst was then washed several times with diethyl ether and water, dried under vacuum, and subsequently reused directly for further catalytic reactions. No significant loss of catalyst ($CuFe_2O_4$) activity was observed up to four cycles.

Based on the preliminary results, various benzyl bromides and alkynes were subjected to the present reaction conditions to investigate the scope and limitation of the reaction. These results are presented in Table 1. Electron donating substituents like methyl, methoxy (entries 3, 10, 14, 15, and 18), and electron withdrawing substituents such as bromo, nitro groups at para position of benzyl bromide (entries 2, 4, 9, 11, 13, and 17) were equally effective toward the nucleophilic substitution of azide, followed by 1,3-dipolar cycloaddition.

When the heterocyclic compound such as 2-ethynylpyridine was used as the alkyne, the reaction proceeded smoothly and the products were isolated in high yields (entries 12–15). In the case of ortho, meta, and para bromo benzyl bromides, all these reacted well to give the corresponding triazoles in near quantitative yields (entries 2, 6, and 7) (steric hindrance has not affected the reaction). However in the case of activated functionalized organic halides such as phenacyl bromide (entry 5), a little low yield of the desired triazole was obtained.

In view of the interesting results obtained with benzyl bromides, the scope of the inexpensive magnetically separable nano copper ferrite catalyzed reaction was extended further to dibromo aliphatic alkanes and aliphatic diacetylenes. The reactions proceeded well to obtain encouraging yields. It was found that terminal dibromoalkane reacts with 2 equiv of alkynes to give bistriazole products (entry 23). Similarly 1,7-octadiyne and 1,8-nonadiyne with 2 equiv of benzyl bromide provided the corresponding bis triazoles (entries 21 and 22).

The reusability of the nano-$CuFe_2O_4$ catalyst was examined and the results are summarized in Table 2. The SEM-analysis of $CuFe_2O_4$ nano particles before and after the reaction showed identical shape and size (Fig. 2).

In conclusion we have developed magnetically separable copper ferrite nanoparticles as a catalyst for the synthesis of 1,2,3-triazoles. This one pot preparation of 1,2,3-triazoles involves initial substitution of benzyl halides with sodium azide to generate in situ benzyl azides which is followed by copper ferrite catalyzed cycloaddition reaction with alkynes in water at 70 °C. The present method described here is simple, facile and can be applicable to a wide range of substrates with high functional group tolerance. The method circumvents the problems encountered with the isolation of organic azides.

The high activity, easy separation, commercial availability, and reusability are the salient features of the catalyst that make this as a competitive catalyst. The operational simplicity of this method makes it more attractive for preparative applications.

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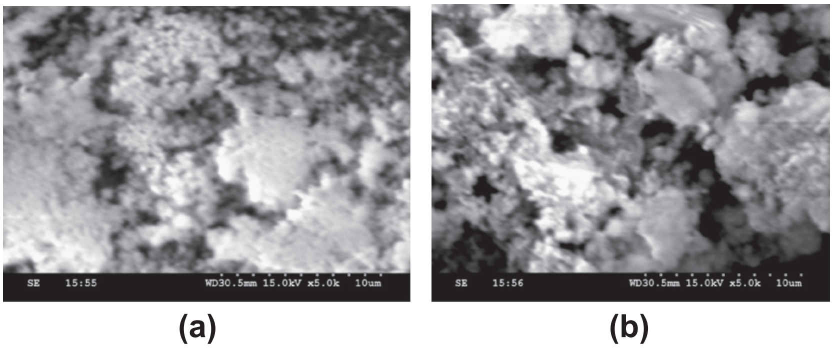

Figure 2. (a) SEM-analysis of native $CuFe_2O_4$ catalyst. (b) SEM-analysis of reused $CuFe_2O_4$ catalyst after 4th cycle.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.077.

References and notes

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21. *Representative procedure*: Benzyl bromide (1 mmol), phenyl acetylene (1 mmol) and NaN_3 (72 mg, 1.1 mmol) were placed in a 10 ml round-bottomed flask in H_2O (2 mL). Sequentially $CuFe_2O_4$ (5 mol %, 12 mg) was added. The reaction mixture was warmed to 70 °C and monitored by TLC until conversion of the starting materials is satisfactory. After completion of the reaction, the reaction mixture was magnetically concentrated with the aid of a magnet to separate the catalyst. Catalyst was separated and washed several times with ether followed by water, dried under vacuum. Water (30 mL) was added to the resulting reaction mixture followed by extraction with EtOAc (4 × 10 mL). The collected organic phases were dried with Na_2SO_4 and the solvent was removed under vacuum to give the corresponding triazole, which did not require any further purification (except compounds **3ga**, **3ha** and **3ii**).
22. *Data of representative example*: 1-Benzyl-4-phenyl-1H-1, 2,3-triazole (Table 1, entry 1): ^1H NMR (300 MHz, $CDCl_3$): δ 5.55 (2H, s), 7.22–7.41 (8H, m), 7.58 (1H, s), 7.75 (2H, d, J = 6.79 Hz). ESI-MS: m/z 236 $(M+H)^+$. HRMS for $C_{15}H_{13}N_3$ Calcd. 236.1187 $(M+H)^+$. Found, 236.1190.