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PAPER

# Synthesis of $\beta$ -Hydroxy-1,4-disubstituted-1,2,3-triazoles catalyzed by Copper ferrite nano particles in tap water using Click Chemistry

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A novel one pot synthesis of  $\beta$ -hydroxy-1,4-disubstituted-1,2,3-triazoles has been developed by using  $\text{CuFe}_2\text{O}_4$  magnetic nano particles. This methodology involves additive free, easily recyclable catalyst in water medium and avoids the handling of organic azides as they are generated *insitu*.

## Introduction

Although homogeneous catalysts have several advantages like higher selectivity and intense interaction among the components in the reaction, the separation of the final product is difficult after completion of the reaction and trace amounts of catalyst may remain in the final product. Since metal contamination is highly regulated in the pharmaceutical industry, it is essential to remove the catalyst from the final compound even if it is in the ppm level. However, heterogeneous catalysts, in particular nano catalysts by their particle size having very large surface area help in enhancing the contact between reactants and catalyst, which can maximize the reaction rates and minimize the consumption of the catalyst to give excellent yields<sup>1</sup>. However, the isolation of these nano particles is not easy through filtration or centrifugation step. It is beneficial, when these catalysts can be separated from the reaction mixture with the aid of an external magnet. In this context, magnetic nano particles (MNPs) have emerged as useful group of heterogeneous catalysts, because of their insoluble and paramagnetic nature<sup>2</sup>.

1, 2, 3-Triazoles are important in heterocyclic chemistry because of their unique structure and chemical properties. Many compounds possessing 1,2,3-triazole structural scaffold exhibit interesting biological properties such as antibacterial, antiviral, antiepileptic, and anti-allergic activities<sup>3,4</sup>. In particular, 1,4-disubstituted 1,2,3-triazoles can be used to selectively open calcium channels in cells<sup>5</sup>, to regulate plant growth<sup>6</sup>, and to inhibit enzymes<sup>7</sup>, as well as exhibit significant antiproliferative action against a wide range of human cancer cell lines<sup>8</sup>.

Sharpless<sup>9</sup> re-invigorated the Huisgen's 1,3-dipolar cycloaddition<sup>10</sup> by using a Cu(I) metal source. These copper-accelerated 1, 3- dipolar cycloadditions enabled efficient preparation of 1, 4-disubstituted-1, 2, 3-triazoles from alkynes and azides with excellent selectivity. Recently a few procedures have been reported for the synthesis of  $\beta$ -hydroxy triazoles by the opening of epoxides in presence of homogeneous catalysts like  $\text{CuSO}_4$ <sup>11</sup> or  $\text{CuI}$ <sup>12</sup>. Francisco Alonso<sup>13</sup> and Patrick Pale<sup>14</sup> have developed separately laboratory-made copper nano particles on activated carbon and Cu (I)-zeolite catalytic method to afford 1, 4-disubstituted  $\beta$ -hydroxy triazoles. Since the resulting products possess a 1-(hydroxyethyl)-1H-1,2,3-triazole moiety which is present in peptide surrogates of HIV-1 protease inhibitors AB2, AB3 (Figure 1) and also useful in drugs and pharmaceuticals<sup>15</sup>, there is a need to develop a simple and efficient method by using a readily available and reusable heterogeneous catalyst in green solvent.

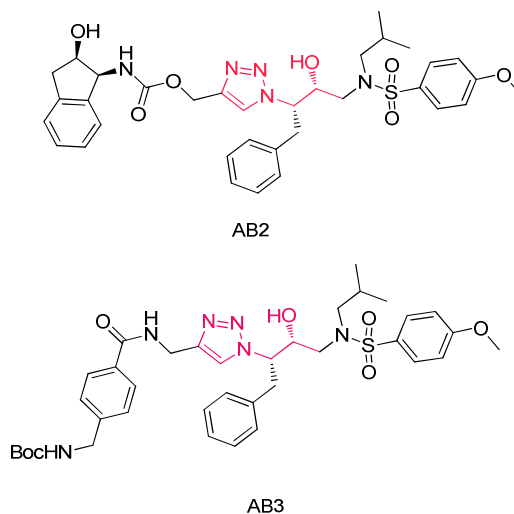


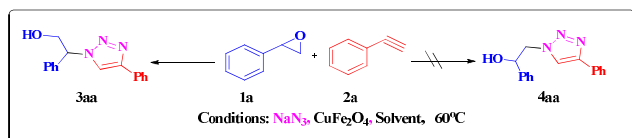
Figure 1. AB2 (pdb-1zp8) and AB3 (pdb-1zpa)

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In continuation of our research interest in the synthesis of heterocyclic compounds using green synthetic protocols involving transition metal catalyst<sup>16</sup>, a copper ferrite catalyzed one pot synthesis of 1, 4-disubstituted-1, 2, 3-triazoles from 5 benzyl halides, sodium azide, and alkynes<sup>17</sup> is developed. Furthermore, in this context, we hereby report copper ferrite MNPs (Purchased from Aldrich-CAS No. 12018-79-0) catalyzed one-pot synthesis of  $\beta$ -hydroxytriazoles from epoxides, sodium azide, and alkynes in aqueous medium. The present protocol 10 satisfies most of the green chemistry principles such as (a) one pot multi component synthesis, (atom economy) (b) reactions in water medium, (green solvent) (c) use of easily separable and recyclable heterogeneous catalyst with the help of an external magnet, (d) simple workup procedure.

## 15 Results and Discussion



Initially,  $\text{CuFe}_2\text{O}_4$  catalyzed reaction between styrene 20 oxide **1a** (1 mmol) and phenyl acetylene **2a** (1 mmol) was investigated to optimise the reaction conditions in various solvents (**Scheme 1**). Among different solvents examined (Table 1), water yielded the best results (entry 2), where as MeOH and MeOH:H<sub>2</sub>O (1:1) gave the products in moderate yields (entries 1 and 7). Solvents such as DMSO, DMF, THF and toluene were ineffective (entries 3,4,6 and 8). The influence of the amount of catalyst and sodium azide was also evaluated. It was observed that the best yield was obtained using 5 mol% of catalyst and 1.1 mmol of  $\text{NaN}_3$  (entries 9, 10, 11, 12 and 13).

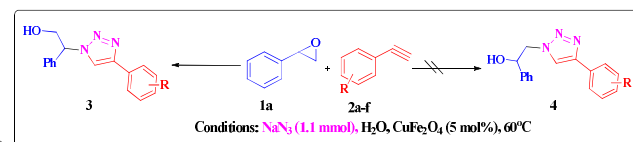
30 **Table 1:** Optimization studies for the synthesis of  $\beta$ -hydroxy-1,4-disubstituted-1,2,3-triazoles

| Entry           | Catalyst (mol%) | $\text{NaN}_3$ (mmol) | Solvent                     | Yield <sup>b</sup> (%) |
|-----------------|-----------------|-----------------------|-----------------------------|------------------------|
| 1               | 5               | 1.1                   | MeOH                        | 45                     |
| 2               | 5               | 1.1                   | H <sub>2</sub> O            | 87                     |
| 3               | 5               | 1.1                   | DMSO                        | 0                      |
| 4               | 5               | 1.1                   | DMF                         | Trace                  |
| 5               | 5               | 1.1                   | EtOH                        | 30                     |
| 6               | 5               | 1.1                   | THF                         | Trace                  |
| 7               | 5               | 1.1                   | MeOH:H <sub>2</sub> O (1:1) | 68                     |
| 8               | 5               | 1.1                   | Toluene                     | 0                      |
| 9               | 1               | 1.1                   | H <sub>2</sub> O            | 42                     |
| 10              | 2               | 1.1                   | H <sub>2</sub> O            | 49                     |
| 11              | 10              | 1.1                   | H <sub>2</sub> O            | 87                     |
| 12              | 5               | 1.0                   | H <sub>2</sub> O            | 71                     |
| 13              | 5               | 1.5                   | H <sub>2</sub> O            | 87                     |
| 14              | 5               | 1.1                   | -                           | 0                      |
| 15 <sup>c</sup> | 5               | 1.1                   | H <sub>2</sub> O            | 69                     |
| 16 <sup>d</sup> | 5               | 1.1                   | H <sub>2</sub> O            | 86                     |

<sup>a</sup>Reaction conditions: styreneoxide (1 mmol), phenyl acetylene (1 mmol),  $\text{NaN}_3$  (1.0-1.5 mmol),  $\text{CuFe}_2\text{O}_4$ (1-10 mol%) in H<sub>2</sub>O (10 mL) at 60 °C for 6 hr.

<sup>b</sup> isolated yields, <sup>c</sup> at 40 °C, <sup>d</sup> at 80 °C

With the optimal conditions in hand, styrene oxide (**1a**) 35 was treated with sodium azide and phenyl acetylene (**2a**) in the presence of 5 mol% of  $\text{CuFe}_2\text{O}_4$  in 10 ml of water at 60 °C (**Scheme 2**). The reaction proceeded smoothly to give the corresponding  $\beta$ -hydroxy-1, 4-disubstituted 1, 2, 3-triazole (**3aa**)



**Table 2:** One pot synthesis of  $\beta$ -hydroxy triazoles using  $\text{CuFe}_2\text{O}_4$  nano particles in water from various epoxides, sodium azide and alkynes<sup>a</sup>

| Entry | Epoxide <b>1</b> | Alkyne <b>2</b> | Triazole <b>3</b> | t (h) | Yield <sup>b</sup> (%) |
|-------|------------------|-----------------|-------------------|-------|------------------------|
| 1     |                  |                 |                   | 6     | 87                     |
| 2     |                  |                 |                   | 6     | 84                     |
| 3     |                  |                 |                   | 8     | 80                     |
| 4     |                  |                 |                   | 7     | 77                     |
| 5     |                  |                 |                   | 6     | 79                     |
| 6     |                  |                 |                   | 7     | 85                     |
| 7     |                  |                 |                   | 5     | 87                     |
| 8     |                  |                 |                   | 6     | 81                     |
| 9     |                  |                 |                   | 6     | 84                     |
| 10    |                  |                 |                   | 7     | 78                     |
| 11    |                  |                 |                   | 6     | 82                     |
| 12    |                  |                 |                   | 4     | 76                     |

| Entry | Epoxide 1 | Alkyne 2 | Triazole 3 | t (h) | Yield <sup>b</sup> (%) |
|-------|-----------|----------|------------|-------|------------------------|
| 13    |           |          |            | 6     | 84                     |
| 14    | 1c        |          |            | 7     | 79                     |
| 15    | 1c        |          |            | 7     | 83                     |
| 16    | 1c        |          |            | 8     | 80                     |
| 17    | 1c        |          |            | 6     | 82                     |
| 18    | 1c        |          |            | 8     | 79                     |
| 19    |           | 2a       |            | 6     | 86                     |
| 20    | 1d        | 2c       |            | 7     | 83                     |
| 21    | 1d        | 2d       |            | 7     | 85                     |
| 22    |           | 2a       |            | 9     | 74 <sup>c</sup>        |

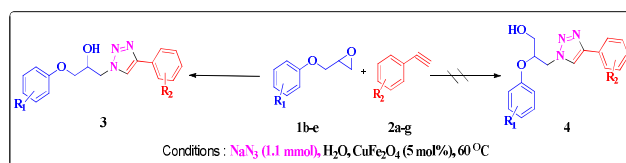
a. Reaction conditions: Alkyne (1 mmol), Epoxide (1 mmol), NaN<sub>3</sub> (1.1 mmol), CuFe<sub>2</sub>O<sub>4</sub> (5 mol%) in H<sub>2</sub>O (10 mL) at 60° C.

b. Isolated yield.

c. Phenyl acetylene (2 mmol)

in high yield. Based on the literature reports,<sup>12,13</sup> among the two possible regional isomers, it was observed that the present product was exclusively primary β-hydroxy triazole (3aa) which was obtained from the styrene oxide by benzylic position opening.

The scope of this copper ferrite catalyzed click reaction was further expanded with a variety of oxiranes and alkynes and these results were summarized in Table 2. The reactions proceeded well to obtain products in encouraging yields. Electron donating substituents like tertiary butyl, as well as methyl group at para position (entries 3 and 4) and electron withdrawing fluorine atom at meta position of phenyl acetylene (entry 5) did not induce appreciable changes in the reaction efficiency. The presence of heterocyclic moiety in the alkynes was equally effective towards the opening of epoxide, followed by 1, 3-dipolar cycloaddition (entry 2).



**Scheme 3**

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The reactivity of glycidyl phenyl ether (entries 7 to 12) and aryl substituted glycidyl phenyl ethers was further explored and examined (**Scheme 3**). These epoxides gave a single regioisomer (3ba) with preferential attack at the less hindered terminal carbon atom which was confirmed by the reported literature<sup>12, 13</sup>.

Both para methoxy as well as ortho methyl substituted glycidyl phenyl ethers also reacted effectively (entries 13 to 22). The reaction between glycidyl phenyl ether and aliphatic 1-octyne (entry 12) resulted in the product in an encouraging yield. It was observed that 1, 4-bis oxirane also reacted with two equivalents of phenyl acetylene providing bis triazole product (entry 22).

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## Recycling

**Table 3:** Recyclability of nano CuFe<sub>2</sub>O<sub>4</sub> catalyst

| Cycle  | Isolated product yield (%) | Catalyst recovery (%) |
|--------|----------------------------|-----------------------|
| Native | 87                         | 91                    |
| 1      | 85                         | 89                    |
| 2      | 82                         | 86                    |
| 3      | 80                         | 81                    |

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Reaction conditions: phenyl acetylene (1 mmol), styrene oxide (1 mmol), NaN<sub>3</sub> (1.1 mmol), CuFe<sub>2</sub>O<sub>4</sub> (5 mol%) in H<sub>2</sub>O (10 mL) at 60° C

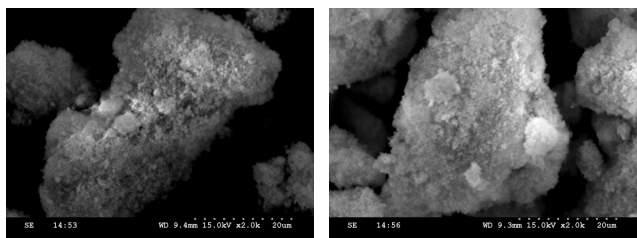
CuFe<sub>2</sub>O<sub>4</sub> catalyst was easily separated by using an external magnet from the reaction mixture (**Figure 2**), washed with acetone and dried under vacuum. The air dried catalyst was used directly for the next cycles without further purification. As shown in Table 3, catalyst could be reused four times without significant changes.

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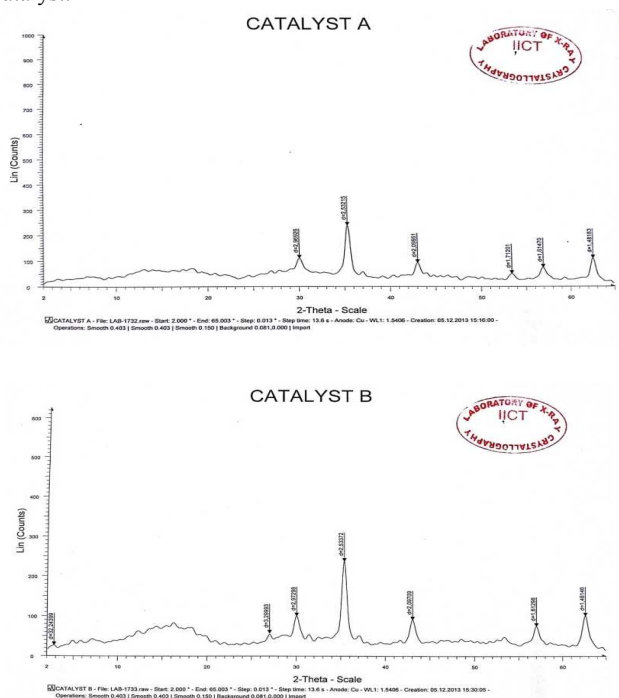
**Figure 2.** Separation of CuFe<sub>2</sub>O<sub>4</sub> nano particles by using an external magnet

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**Figure 3.** (a) SEM-analysis of native  $\text{CuFe}_2\text{O}_4$  catalyst. (b) SEM-analysis of reused  $\text{CuFe}_2\text{O}_4$  catalyst after 4<sup>th</sup> cycle

The SEM images of the catalyst exhibited identical shape and size (**Figure 3**) and the XRD analysis also indicated similar peaks for both native and recycled catalyst (**Figure 4**). These results clearly support nearly unaltered efficiency of the catalyst.



**Figure 4.** XRD spectra of  $\text{CuFe}_2\text{O}_4$  catalyst (a) native and (b) after the 4<sup>th</sup> cycle.

## Conclusions

In conclusion, an efficient green protocol is developed for the synthesis of  $\beta$ -hydroxy 1, 2, 3-triazoles from epoxides, sodium azide and alkynes in aqueous medium. The advantages of the present protocol are (a) one pot three component 1, 3 dipolar alkyne-azide cyclo addition, which involves the *in situ* generation of organic azides by using low cost sodium azide in water medium as it avoids the isolation of hazardous organic azides, (b) reduction in the number of steps and waste generation, which improves the overall yield and reduces the reaction time and operational procedures, (c) ease of recyclability of  $\text{CuFe}_2\text{O}_4$  magnetic nano particles, (d) use of universally acceptable green solvent-water medium without any additives at 60°C. This method is simple, facile and applicable to a wide range of epoxides and alkynes with high functional group tolerance.

## Experimental Section

**General Experimental Procedure:** Styrene Oxide (1 mmol), phenyl acetylene (1 mmol) and  $\text{NaN}_3$  (72 mg, 1.1 mmol) were placed in a 25 ml round-bottomed flask in  $\text{H}_2\text{O}$  (10 mL), to which  $\text{CuFe}_2\text{O}_4$  (5 mol %) was added. The reaction mixture was warmed to 60 °C and monitored by TLC until total conversion of the starting materials. After completion of the reaction, the catalyst was separated with the aid of a magnet. The separated catalyst was washed several times with acetone, dried under vacuum. The reaction mixture was extracted with EtOAc (4x10 mL), the collected organic phases were dried with  $\text{Na}_2\text{SO}_4$  and the solvent was removed under vacuum to give the corresponding triazole derivative. Further, products were purified by column chromatography using hexane and ethyl acetate.

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