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**Research Article**

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# (1-(4-Methoxybenzyl)-1-*H*-1,2,3-triazol-4-yl)methanol (MBHTM) accelerated copper-catalyzed [3+2] azide-alkyne cycloaddition (CuAAC) at low catalyst loading in PEG-$H_2O$ as green reaction media

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**ABSTRACT**

*Facile synthesis of diverse 1,4-disustituted 1,2,3-triazoles derivatives using readily accessible, cost effective, remarkably stable and easily tunable 1,2,3 triazole based ligand,* ***(1-(4-Methoxybenzyl)-1-H-1,2,3-Triazol-4-yl)Methanol (MBHTM)*** *in PEG-$H_2O$ as green reaction media has been developed . As compared to ligand free reaction, the dramatic rate enhancement of copper catalyze azide–alkyne cycloaddition (CuAAC) at low catalyst loading in PEG-$H_2O$ media has been observed. The present method provides high to excellent yields and thus considered to be the green "click chemistry" tool for synthetic applications.*

**Keywords:** Click Chemistry, Ligand, 1,2,3-triazoles, Polyethylene glycol, Cycloaddition.

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## INTRODUCTION

With increasing environmental concerns and regulatory constraints faced by chemical and pharmaceutical industries, the development of green protocol in organic synthesis has become one of the frontiers in organic chemistry research. The use of green reaction media such as the water, ionic liquids, flourous media, supercritical fluids and Polyethylene glycol and derivatives for chemical process is always advisable from the perspective of green chemistry. In recent years PEG [1] and its derivatives has attracted much attention of synthetic chemist as reaction media due it low cost, stability and environmentally benign nature. Moreover PEG is nontoxic and been already approved by FDA for oral applications. Thus, the use of PEG as reaction media provides ecological and economical synthetic protocols.

The Huisgen[2] first of all reported the 1,3-dipolar cycloaddition of alkynes to azides to form 1,4-disubsituted-1,2,3-triazoles, Following the discovery by Huisgen, Sharpless *et al*.[3] and Meldal *et a*l[4] in 2002 reported that the copper(I) catalyzes the 1,3-dipolar cycloaddition of azides and alkynes to form 1,4-disubstituted triazoles (CuAAC). Following this discovery, CuAAC has rapidly emerged as powerful tool for the construction of 1, 2, 3 –triazole scaffold. It has been also found that ligand play the prominent role in the rate acceleration of CuAAC. Thus the ligand not only stabilizes the oxidation state of Cu(I), but shown to increase and modulate its reactivity and thus providing the effective catalytic system through the catalytic cycle.[5]

As a result, recently to further advance the scope of CuAAC tremendous efforts have been placed on the ligand acceleration this reaction. Various ligand systems have been tested to promote the rate acceleration of CuAAC. These include polytriazolylamine (TBTA) [6] and is the most preferred even today, benzimidazoles, [7] histidine derivatives,[8] pybox ligands,[9] phosphites,[10] and NHC carbenes.[11] Most of these ligands show rate acceleration,while many of them suffer from the limitations such as long reaction time, high cost and lack of tunability[12]. Moreover, the applicability of efficient ligands such as NHC carbines has been limited by their challenging synthetic routes. Recently, Feringa *et al*. [13] reported highly efficient BINOL based phosphoramidite accelerated copper(I)-catalyzed [3 + 2 ] cycloadditions of azides and alkyne. Thus despite of these, efforts, as compared to other metal catalysed reaction, the focused on developing more efficient catalytic system for CuAAC remained limited.

The 1, 2, 3 –triazole could be readily syntheised via CuAAC reaction; they are remarkable stable, inexpensive and readily tunable. The 1, 2, 3-triazole have been reported to be highly effective ligands for transition and late transition metal complexes.

We had previously reported (1-(4-methoxybenzyl)-1-H-1, 2, 3- triazol-4-yl) methanol (MBHTM)[14] accelerated copper-catalyzed [3+2] azide–alkyne cycloaddition (CuAAC)[14] at low catalyst loading. However, the use of DMSO as solvent, particularly from the perspective of green chemistry limits the applicability of this protocol and there is enough scope for the improved protocol for CuAAC. We reason that the use of PEG in combination with water assuming high solubilising power of PEG for organic substrates could provide green alternative for the copper-catalyzed [3+2] azide–alkyne cycloaddition (CuAAC) leading to the synthesis of diverse 1,2,3-triazole derivatives.

Herein we report for the first time that the readily accessible, cost effective, easily tunable and simple but powerful "Click" ligand, MBHTM, synthesized itself by click chemistry [15] dramatically accelerates the copper catalyse [3+2] cycloaddition of azide and alkyne at low copper catalyst loading in PEG-$H_2O$ as green reaction media at ambient conditions.

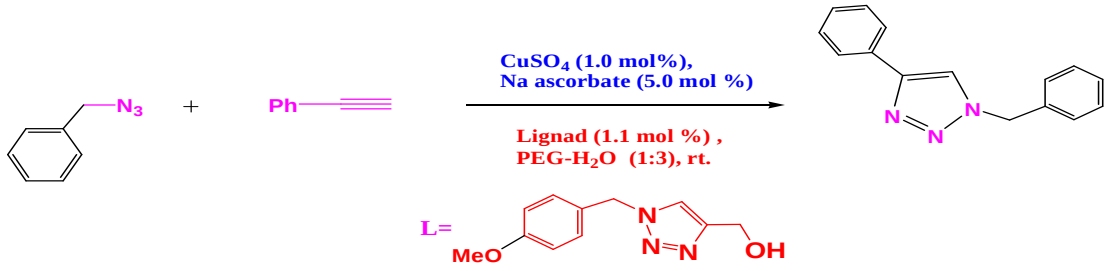
## EXPERIMENTAL SECTION

All the solvents were redistilled before used. Analytical TLCs were performed on Merck silica gel 60F254 plates. The alkynes were purchased from Johnson Matthey Chem. Ltd and other chemicals were purchased from Sigma Aldrich Chem. Ltd. The $^{1}H$ and $^{13}C$ NMR spectra (in $CDCl_3$) were recorded on Agilent 400 or Bruker Avance-II 400 MHz spectrometer. The chemical shift values are on scale and TMS was used as an internal standard. Abbreviations used are: s (singlet), d (doublet), t (triplet), dd (double doublet), dt (doublet triplet), m (multiplet).

To a 10 mL vial charged with copper sulfate (0.5 mg, 0.01 mmol), sodium ascorbate (2 mg, 0.05 mmol) and ligand (1.1 mol %) was added 0.5 mL of PEG-$H_2O$ mixture (1:3) and resulting mixture was stirred at room temperature for 10 min. Then the appropriate azide (0.2 mmol) and alkyne (0.4 mmol, 2.0 equiv.) was added to it and the reaction mixture was stirred vigorously at room temperature for 6h. After completion of reaction (TLC), the reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (3x10 mL) and combined organic extract was washed several times with water and then with brine. Evaporation of organic extract after drying over anh. $Na_2SO_4$ followed by column chromatography (PET:EA, 7:3) afforded analytically pure 1, 2, 3-triazole derivatives.

## RESULTS AND DISCUSSION

Embarking on our previous results, we initially chose the model reaction between benzyl azide and phenyl acetylene in order to check the ligand effect, if any, in PEG-$H_2O$ as the solvent system**. Scheme-1.**




**Scheme -1**

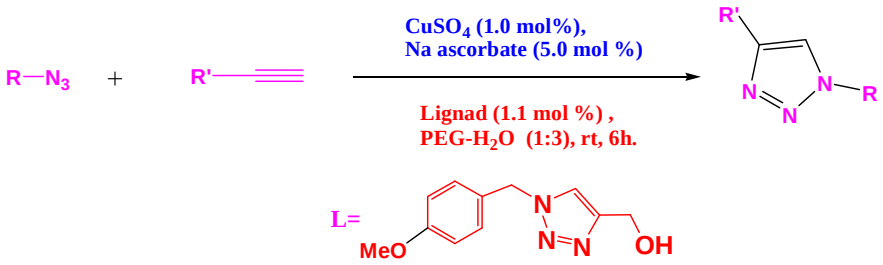
**Table-1: Optimization conditions for copper catalyzed [3+2] Azide-Alkyne Cycloaddition in PEG: $H_2O$[a]**

| Entry | Time (h) | Yield (%)[b] |
|---|---|---|
| 1 | 1 | 39 |
| 2 | 2 | 55 |
| 3 | 3 | 75 |
| 4 | 6 | 85 |
| 5 | 6 | 96[c] |
| 6 | 24 | 36[d] |

*[a] Reaction conditions: 0.2 mmol of benzyl azide, 0.2 mmol of phenyl acetylene, 1.0 mol % of copper salt, 5.0 mol % Na-ascorbate in presence of 1.1 mol % of ligand in 0.5 ml PEG-$H_2O$ (1:3) at room temperature. [b]Isolated yields. [c] 2 equiv of alkyne was used. [d] in the absence of ligand*

The reaction time was kept somewhat higher than that of our optimized reaction time of 4h in our previous work assuming that PEG-$H_2O$ system would have relatively lower solubilising power than DMSO. Thus using our MBHTM ligand m the model reaction was explored with varying reaction time from 1 to 6h. We found that as compared to ligand-free reaction, the present ligand found to accelerate the CuAAC reaction dramatically as evident by 36 % and 96% yield of ligand free and ligand promoted reaction (table-1, entry **6** vs **5**) respectively. The best results were obtained when the reaction was run for 6 h.

Thus the best reaction conditions were found to be 1.0 equiv. of azide, 2.0 equiv. of alkyne, 1.0 mol % of $CuSO_4$, $5H_2O$, 5 mol % of Na-ascorbate in the presence of 1.1 mol % of ligand in PEG-Water at room temperature for 6 h. Using our optimized reaction conditions as described above, next, scope of the reaction was explored with diverse azides and alkynes scheme-**2**.




**Scheme-2**

Thus the wide variety of azide and alkynes were subjected to CuAAC reaction facilitated by our novel ligand (1-(4-methoxybenzyl)-1-H-1, 2, 3- triazol-4-yl) methanol (MBHTM) using PEG-$H_2O$ system.

As can be seen from results **(table-2**), a wide range of alkynes such as phenylacetylene derivatives, aliphatic, and heterocyclic alkynes reacted rapidly giving high to near quantitative yields.[16] Several phenoxymethyl alkynes such as (4-Bromophenoxy)methyl, 4-(Ethylphenoxy) methyl acetylenes etc. were also reacted smoothly under present reaction conditions. The presence of electron withdrawing or electron releasing substituent on the benzene ring did not affect the reactivity strikingly as theses alkynes provided the 1,2,3-triazole products in high to excellent yields.

**Table-2: Scope of the Azide and alkynes in CuAAC in PEG: Water[a]**

| Entry | Alkyne | Azide | Product | Yield (%)[b] |
|---|---|---|---|---|
| 1 | 1a | 2a | 3a | 96 |
| 2 | 1b | 2a | 3b | 87 |
| 3 | 1c | 2a | 3c | 92 |
| 4 | 1d | 2a | 3d | 90 |
| 5 | 1e | 2a | 3e | 97 |
| 6 | 1f | 2a | 3f | 95 |
| 7 | 1a | 2b | 3g | 64 |
| 8 | 1a | 2c | 3h | 54 |
| 9 | 1a | 2d | 3i | 38 |
| 10 | 1g | 2d | 3j | 94 |
| 11 | 1a | 2e | 3k | 94 |
| 12 | 1a | 2f | 3l | 35 |
| 13 | 1h | 2a | 3m | 75 |

*Reaction conditions: 0.2 mmol of benzyl azide, 0.4 mmol of phenyl acetylene (2.0 equiv.), 1.0 mol % of copper salt, 5.0 mol % Na-ascorbate in presence of 1.1 mol % of ligand in 0.5 ml PEG-$H_2O$ (1:3) at room temperature.* [b]*Isolated yields by column chromatography.*

Similar to previous results, the aliphatic alkynes such as 1-pentyne and 3-methyl non-1-yn -3-ol reacted quickly to give with very high yields. Even the cyclic alkynes such as ethynylcyclopropane reacted efficiently with excellent yield under these conditions without giving any side products. The novel alkynes specially designed such as 1-(prop-2-ynyl)-indoline-2,3-dione also converted to the corresponding (1-triazolylmethyl)indoline-2,3-dione) in good yield. As regard to the azide, the azides such as the aromatic and benzylic azides bearing both the electron rich as well as electron deficient substituent such alkyl, halides, cyano, nitro- etc. found to be suitable substrate for the present reaction and they afforded good to high yield of the corresponding 1,2,3-triazole products. However, the arylazides shown relatively low reactivity than benzylic azides but they furnished good yields under present conditions.

Notably, the novel triazolyl azide, 4-(azidomethyl)-1-benzyl-1H-1,2,3-triazole was also converted to the corresponding 1-benzyl-4-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)-1H-1,2,3-triazole in moderate yield using this protocol .

Thus we have developed novel, an efficient, and green protocol for the synthesis of diverse 1,2,3-trizole derivatives via Ligand accelerated CuAAC reaction using PEG-water as green reaction media. The low catalyst loading, broad substrate scope of azide and alkynes, short reaction time and high to excellent yield makes this protocol potentially useful in synthetic chemistry.

**Analytical data of 1,2,3-triazole derivatives:**

**1-benzyl-4-phenyl-1H-1,2,3-triazole(3a)**

$^1$HNMR: ($CDCl_3$, 400 MHz): δ 5.56 (s, 2H), 7.28-7.32 (m, 3H), 7.34-7.40 (m, 5H), 7.65 (s, 1H), 7.77 (tt, 2H). $^{13}$C NMR: ($CDCl_3$, 400 MHz): δ 54.2, 119.5, 125.7, 128.0, 128.1, 128.8, 129.1, 130.5, 134.7, 148.2

**4-(4-tert-butylphenyl)-1-benzyl-1H-1,2,3-triazole(3b)**

$^1$H NMR: ($CDCl_3$, 400 MHz): δ 1.32 (s, 9H), 5.56 (s, 2H), 7.27-7.29 (m, 2H), 7.34-7.38 (m, 3H), 7.40 (tt, 2H). $^{13}$C NMR: ($CDCl_3$, 400 MHz): δ 31.2, 34.6, 54.1, 119.2, 125.4, 125.7, 127.7, 128.0, 128.7, 129.1, 134.8, 148.2, 151.2

**4-((4-ethylphenoxy)methyl)-1-benzyl-1H-1,2,3-triazole(3c)** $^1$H NMR: ($CDCl_3$, 400 MHz): δ 1.18 (t, 3H), 2.55 (q, 2H), 5.16 (s, 2H), 5.52 (s, 2H), 6.87 (dd, 2H), 7.08 (d, 2H), 7.25-7.28 (dt, 2H), 7.35-7.38 (m, 3H), 7.51 (s, 1H). $^{13}$C NMR: ($CDCl_3$, 400 MHz): δ 15.8, 27.9, 54.2, 62.2, 114.6, 122.5, 128.1, 128.7, 128.8, 129.1, 134.5, 137.0, 144.9, 156.2

**4-((4-bromophenoxy)methyl)-1-benzyl-1H-1,2,3-triazole(3d)**

$^1$HNMR: ($CDCl_3$, 400 MHz): δ 5.14 (s, 2H), 5.52 (s, 2H), 6.82 (tt, 2H), 7.25 (dt, 2H), 7.33-7.40 (m, 5H), 7.50 (s, 1H). $^{13}$C NMR ($CDCl_3$, 400 MHz): δ 54.2, 62.2, 113.5, 116.6, 122.6, 128.1, 128.8, 129.1, 132.3, 134.3, 144.1, 157.2

**1-benzyl-4-cyclopropyl-1H-1,2,3-triazole(3f)**

$^1$HNMR: ($CDCl_3$, 400 MHz): δ 0.79-0.85 (m, 2H), 0.88-0.93 (m, 2H), 1.87-1.94 (m, 1H), 5.45 (s, 2H), 7.14 (s, 1H), 7.23-7.27 (m, 2H), 7.33-7.38 (m, 3H). $^{13}$C NMR: ($CDCl_3$, 400 MHz): δ 6.7, 7.7, 53.9, 119.5, 127.9, 128.6, 129.0, 134.9, 150.6

**1-(4-bromobenzyl)-4-phenyl-1H-1,2,3-triazole(3g)**

$^1$H NMR: ($CDCl_3$, 400 MHz): δ 5.52 (s, 2H), 7.16 (d, 2H), 7.30-7.34 (m, 1H), 7.38 (ddd, 2H), 7.49 (tt, 2H), 7.66 (s, 1H), 7.78-7.80 (m, 2H). $^{13}$C NMR: ($CDCl_3$, 400 MHz): δ 55.5, 119.4, 122.9, 125.7, 128.3, 128.8, 129.6, 130.3, 132.3, 133.7, 148.4

**1-(4-nitrobenzyl)-4-phenyl-1H-1,2,3-triazole(3h)**

$^1$HNMR: ($CDCl_3$, 400 MHz): δ 5.70(s, 2H), 7.32-7.36 (m, 1H), 7.40-7.46 (m, 4H), 7.74 (s, 1H), 7.80 (dt, 2H), 8.23 (dt, 2H).

**4-phenyl-1-p-tolyl-1H-1,2,3-triazole(3i)**

$^1$H NMR: ($CDCl_3$, 400 MHz): δ 2.34 (s, 3H), 7.23-7.29 (m, 3H), 7.35- 7.39 (m, 2H), 7.56 (dd, 2H), 7.80 (tt, 2H), 8.07(s, 1H). $^{13}$C NMR: ($CDCl_3$, 400 MHz): δ 21.1, 117.6, 120.4, 125.8, 128.3, 128.9, 130.2, 130.3, 134.8, 138.9, 148.2

**2-(1-p-tolyl-1H-1,2,3-triazol-4-yl)octan-2-ol(3j)**

$^1$H NMR: ($CDCl_3$, 400 MHz): δ 0.83 (t, 3H), 1.25-1.35 (m, 8H), 1.65 (s, 3H), 1.90-1.96 (m, 2H), 2.41 (s, 3H), 2.96 (br, 1H), 7.26 (d, 2H), 7.58 (tt, 2H), 7.84 (s, 1H). $^{13}$C NMR: ($CDCl_3$, 400 MHz): δ 14.0, 21.0, 22.6, 23.9, 28.5, 29.55, 31.7, 43.2, 71.1, 117.9, 120.3, 130.1, 134.1, 138.7, 155.4

**4-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)benzonitrile(3j)**

$^1$H NMR: ($CDCl_3$, 400 MHz): δ 5.63 (s, 2H), 7.31-7.43 (m, 5H), 7.64 (dd, 2H), 7.74 (s, 1H), 7.78 (tt, 2H). $^{13}$C NMR: ($CDCl_3$, 400 MHz): δ 53.4, 112.7, 118.1, 119.7, 125.7, 128.3, 128.4, 128.9, 130.1, 132.9, 139.9, 148.6

## CONCLUSION

In conclusion, we have demonstrated herein that the novel, easily accessible, highly stable, tunable and inexpensive 1,2,3,-triazole ligand, (1-(4-Methoxybenzyl)-1-*H*-1,2,3-Triazol-4-yl)Methanol (MBHTM), dramatically accelerate the rate of CuAAC at low catalyst loading in PEG-Water as environmentally benign reaction media. The low catalyst and ligand loading, high to excellent yields, use of PEG-Water as green reaction media, broad substrate scope coupled with mild reaction conditions employed here makes the present protocol potentially useful in organic synthesis.

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[15] To a 10 mL flask charged with copper sulphate (5 mol %) and Na-ascorbate (10 mol%) was added 2 mL of t-butanol;water (1:3) and mixture was stirred at room temperature for 10 minutes, then 4-methoxybenzyl azide (1 mmol), propargyl alcohol (1.1 mmol, 1.1 equiv.) was added to the above mixture and stirred overnight. After completion of the reaction (TLC), the reaction mixture was quenched with water and extracted with ethyl acetate (3x 5 mL). The combined organic extract was dried over anhydrous sodium sulphate, solvent evaporated under reduced pressure. The column chromatography of the crude product afforded the title compound in 41 % yield. (Eluent: 100% ethyl acetate).
[16] To a 10 mL vial charged with copper sulfate (0.5 mg, 0.01 mmol), sodium ascorbate (2 mg, 0.05 mmol) and ligand (1.1mol %) was added 0.5 mL of PEG-$H_2O$ mixture (1:3) and resulting mixture was stirred at room temperature for 10 min. Then the appropriate azide (0.2 mmol) and alkyne (0.4 mmol, 2.0 equiv.) was added to it and the reaction mixture was stirred vigorously at room temperature for 6h. After completion of reaction (TLC), the reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (3x10 mL) and combined organic extract was washed several times with water and then with brine. Evaporation of organic extract after drying over anh. $Na_2SO_4$ followed by column chromatography (PET:EA, 7:3) afforded analytically pure 1, 2, 3-triazole derivatives.