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# A New Paradigm of Copper Oxide Nanoparticles Catalyzed Reactions: Synthesis of 1,2,3-Triazoles Through Oxidative Azide-Olefin Cycloaddition

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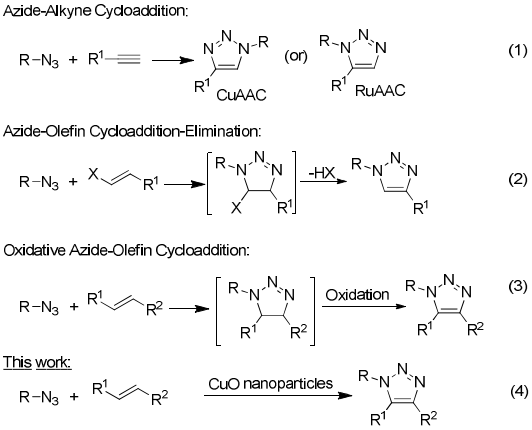
**Heterogeneous CuO nanoparticles catalyzed oxidative [3+2] cycloaddition of organic azides with a variety of activated olefins is described. A diverse array of 1,4-disubstituted and 1,4,5-trisubstituted 1,2,3-triazoles have been achieved in moderate to excellent yields.**

After the evolution of 'Click reactions',[1] 1,2,3-Triazole motif has sprung into prominence opening up new horizons in various fields such as supramolecules,[2] polymers,[3] functional coatings[4] and chemical synthesis.[5] Most importantly, they display a wide spectrum of biological activities such as anti HIV, anticancer, antiviral, antifungal and antibacterial activities.[6] In the beginning, 1,2,3-triazoles were accessed by the conventional Huisgen 1,3-dipolar cycloaddition between azides and alkynes.[7] Despite being a genuine avenue to achieve the azide-alkyne cycloaddition ensuring 100% atom economy, it could not overcome the stumbling blocks such as poor regioselectivity and high thermal requirements. These limitations were circumvented by copper-catalyzed azide-alkyne cycloaddition (CuAAC) and ruthenium-catalyzed azide-alkyne cycloaddition (RuAAC) [Eq. (1), Scheme 1].[8,9] However CuAAC is selective towards 1,4-disubstituted triazoles and limited to terminal alkynes. Whereas RuAAC leads to the complementary 1,5-disubstituted triazoles and works out for internal alkynes as well. In continuation, few more methods also have been reported on the cycloaddition of azides with internal alkynes to achieve 1,4,5-trisubstituted 1,2,3-triazoles.[10]

As an alternative strategy to azide-alkyne cycloaddition, olefins were envisaged in the place of alkynes to access 1,2,3-triazole derivatives. Pioneer research on azide-olefin cycloaddition (AOC) was carried out by Huisgen and L'abbe[11] with azides and electron deficient olefins to form triazolines. These triazolines are generally unstable and they often crumble into different products depending upon the reaction conditions.[12] Nevertheless, methods to aromatize this unstable triazolines into stable triazolines were sought out by a few research groups. In this regard, olefins bearing the leaving groups were anticipated to furnish the required triazoles by cycloaddition followed by subsequent elimination reaction [Eq. (2), Scheme 1]. At this juncture, vinyl acetate,[13] nitro olefins,[14] push-pull olefins[15] and vinyl sulfones[16] were subjected to cycloaddition-elimination sequence with various azides to achieve the 1,2,3-triazoles. Another intriguing class of reactions is 'organo click reactions' where enamines obtained *in situ* from various carbonyl and dicarbonyl compounds would undergo cycloaddition-elimination with aromatic azides to accomplish the 1,2,3-triazoles.[17] Recently Ramachary *et al* has reported 1,4-disubstituted 1,2,3-triazoles based on the enolate-mediated organo click reaction of commercially available enolizable aldehydes and aryl azides.[18]




**Scheme 1** Background of oxidative azide-olefin [3+2] cycloaddition.

However, olefin without any leaving group is another potential candidate which is yet to be explored in the azide-olefin cycloaddition chemistry. The resulting triazolines bearing no leaving group can be aromatized into triazoles by its concomitant oxidation [Eq. (3), Scheme 1]. Such oxidative azide-olefin cycloaddition (OAOC) has been attempted by a few research groups. Tripathi *et al* has reported the oxidative cycloaddition of sugar derived azides with chalcones/arylpropenones catalyzed by tetra butyl ammonium hydrogen sulphate (TBAHS).[19] Yao *et al* has reported copper(I) promoted oxidative [3+2] cycloaddition of electron deficient

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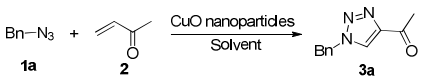
terminal and internal olefins with azides under basic condition and molecular oxygen.[20] Pan and co-workers have reported the $Ce(OTf)_3$ catalyzed oxidative cycloaddition of chalcones and benzylazides.[21]

In addition, *N*-2-aryl-substituted-1,2,3-triazoles through one pot azide-chalcone oxidative cycloaddition and post-triazole arylation also has been reported by a few research groups.[22] Other electron-deficient olefins such as 1,4-benzoquinone[23] and 1,4-naphthaquinone[24] have also been subjected to OAOC with various azides. Nevertheless, all these methods are associated with their own limitations such as high temperature, use of base, long reaction time, poor selectivity, non-reusability of catalyst etc. At this juncture, we envisaged to employ the commercially available and inexpensive CuO nanoparticles[25] [Eq. (4), Scheme 1] as a heterogeneous catalyst for the OAOC.

At the outset, we started our investigation with methyl vinyl ketone and benzyl azide as model substrates for optimizing the OAOC. A rigorous screening of various solvents was carried out and the results are summarized in Table 1. When toluene was employed as the reaction medium, the corresponding triazole was obtained in good yield (Table 1, entry 1). On the other hand, moderate yield of triazole was obtained when benzene was used as the solvent (Table 1, entry 2). Other solvents such as acetonitrile, chloroform and 1,4-dioxane were found to be affecting the efficacy of the reaction which is reflected in the decrement of yields (Table 1, entries 3-5). To our surprise, water was revealed as the best solvent for this transformation furnishing excellent yield (Table 1, entry 6). Tertiary butanol-water mixture also turned out to be the second effective solvent system which is evident from the very high yield registered (Table 1, entry 7). On the contrary, methanol being a polar protic solvent could not follow the trend of water and *t*-butanol/water systems as the yield tremendously dropped down to 40% (Table 1, entry 8). The efficiency diminished further more in case of THF as it led to very poor yield of the product (Table 1, entry 9). It is noteworthy that the polar aprotic solvents such as DMF and DMSO were found to be the least effective solvents for this transformation since only trace amounts of product was detected (Table 1, entries 10-11). Only 25% yield of product was obtained under neat condition (Table 1, entry 12).

**Table 1**. Effect of solvents in OAOC[a]

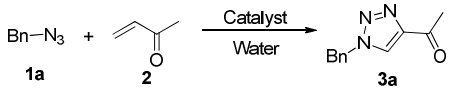



| Entry | Solvent | Yield (%)[b] |
|---|---|---|
| 1 | Toluene | 80 |
| 2 | Benzene | 60 |
| 3 | $CH_3CN$ | 50 |
| 4 | $CHCl_3$ | 46 |
| 5 | 1,4-Dioxane | 45 |
| **6** | **Water** | **99** |
| 7 | t-BuOH/Water (1:1) | 90 |
| 8 | Methanol | 40 |
| 9 | THF | 20 |
| 10 | DMF | Trace |
| 11 | DMSO | Trace |
| 12 | - | 25 |

[a] Reaction conditions: benzyl azide (1.5 mmol), methyl vinyl ketone (4.5 mmol), CuO nanoparticles (20 mol%) and solvent (4 mL) were stirred at room temperature for 8h. [b] Isolated yields.

Having inferred that the water is the best solvent for oxidative azide olefin cycloaddition, we embarked on investigating the role of the catalyst as well. Various bulk catalysts were examined in the place of CuO nanoparticles for the oxidative cycloaddition of benzyl azide and methyl vinyl ketone (Table 2). The bulk catalysts such as $CuCl_2$, $CuSO_4$, $Cu(OTf)_2$, CuCl, CuBr, CuI and copper powder were found to be inferior to CuO nanoparticles to boost the transformation which was confirmed from the yields obtained (Table 2, entries 1-7). Most importantly, even CuO showed distinct difference from its nano sibling (Table 2, entry 8). In addition, the quantity of the CuO nanocatalyst also played a pivotal role in the efficacy of the reaction which is evident from the gradual enhancement of yield while increasing the amount of catalyst from 2 mol% to 20 mol% (Table 2, entries 9-13). Apparently, only trace amount of product was detected when the reaction was carried out in the absence of catalyst (Table 2, entry 14).

**Table 2.** Role of catalyst in OAOC[a]



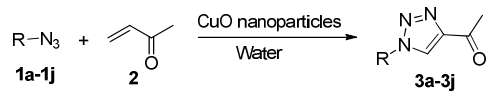

| Entry | Catalyst | Amount of catalyst (mol%) | Yield (%)[b] |
|---|---|---|---|
| 1 | $CuCl_2$ | 20 | 32 |
| 2 | $CuSO_4$ | 20 | 40 |
| 3 | $Cu(OTf)_2$ | 20 | 41 |
| 4 | Cu powder | 20 | 31 |
| 5 | CuCl | 20 | 38 |
| 6 | CuBr | 20 | 32 |
| 7 | CuI | 20 | 54 |
| 8 | CuO | 20 | 25 |
| 9 | CuO nanoparticles | 2 | 30 |
| 10 | CuO nanoparticles | 5 | 41 |
| 11 | CuO nanoparticles | 10 | 54 |
| 12 | CuO nanoparticles | 15 | 67 |
| 13[c] | CuO nanoparticles | 20 | 99 |
| 14 | - | - | Trace |

[a] Reaction conditions: benzyl azide (1.5 mmol), methyl vinyl ketone (4.5 mmol) and water (4 mL) were stirred at room temperature for 8h. [b] Isolated yields.
[c] Reaction with 1.5 mmol of **2** led to 40 % yield of **3a** and 3.0 mmol of **2** furnished 73 % yield of **3a** after 12 h at room temperature.

Having fixed the solvent (water), catalyst (CuO nanoparticles) and the amount of catalyst (20 mol%) from afore mentioned optimization studies, we set out to study the scope of azides with methyl vinyl ketone. Various benzyl, aromatic and aliphatic azides were subjected to the oxidative cycloaddition with methyl vinyl ketone and the results are summarized in Table 3. Benzyl azide (**1a**) gave excellent yield of the required triazole (**3a**) as already mentioned in the optimization studies (Table 3, entry 1). In the case of substituted benzyl azides (**1b**, **1c**, **1d** & **1e**), yield of triazole dropped down significantly (Table 3, entries 2-5). Electron deficient phenyl azide (**1f**) also was able to undergo cycloaddition with good yield like substituted benzyl azides (Table 3, entry 6). Remarkable difference evolved only in the case of aliphatic azides such as phenethyl, *n*-hexyl and *n*-octyl azides as they showed comparatively less yield than benzyl and aromatic azides (Table 3, entries 7-9). Azido-acetic acid ethyl ester (**1j**) being more electron deficient was found to be the least effective among all the aliphatic azides employed here since

the yield declined further more to 61% (Table 3, entry 10).

**Table 3.** Substrate Scope of Azides[a]

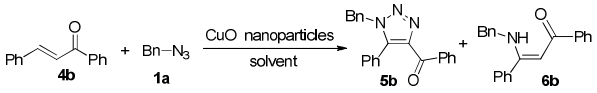



| Entry | R | Azide | Product | Yield (%)[b] |
|---|---|---|---|---|
| 1 | Bn | **1a** | **3a** | 99 |
| 2 | 4-$ClC_6H_4CH_2$ | **1b** | **3b** | 76 |
| 3 | 4-$CH_3C_6H_4$ $CH_2$ | **1c** | **3c** | 78 |
| 4 | 4-$CH_3OC_6H_4CH_2$ | **1d** | **3d** | 80 |
| 5 | 4-$NO_2C_6H_4CH_2$ | **1e** | **3e** | 81 |
| 6 | Ph | **1f** | **3f** | 78 |
| 7 | $C_6H_5CH_2CH_2$ | **1g** | **3g** | 71 |
| 8 | $C_6H_{13}$ | **1h** | **3h** | 68 |
| 9 | $C_8H_{17}$ | **1i** | **3i** | 73 |
| 10 | $C_2H_5OCOCH_2$ | **1j** | **3j** | 61 |

[a] Reaction conditions: Azide (1.5 mmol), methyl vinyl ketone (4.5 mmol), CuO nanoparticles (20 mol%) and water (4 mL) were stirred at room temperature for 8h.[b] Isolated yields.

In continuation, we set out to investigate the scope of olefins employing various electron deficient olefins under the same reaction condition. When we began with ethyl vinyl ketone (**4a**), it furnished good yield of triazole (**5a**) with benzyl azide (Table 5, entry 1). But when we moved on to **4b** which is an internal alkene, no product was detected. When the temperature was raised to 90 °C, the required triazole (**5b**) was obtained with 45% yield. Along with that, Z-β-aryl enaminone (**6b**) was also obtained with 20% yield (Table 4, entry 1).

**Table 4**. Optimization of OAOC of internal olefins[a]

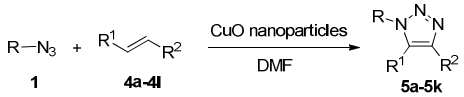



| Entry | Solvent | T (°C) | Amount of **1a** (eq) | Yield of **5** (%)[b] | Yield of **6** (%)[b] |
|---|---|---|---|---|---|
| 1 | $H_2O$ | 90 | 1.5 | 45 | 20 |
| 2 | $H_2O$-$^t$BuOH | 90 | 1.5 | 33 | 12 |
| 3 | $CH_3CN$ | 90 | 1.5 | 23 | <2 |
| 4 | - | 90 | 2.5 | 70 | 21 |
| 5 | Toluene | 90 | 1.5 | 65 | 0 |
| **6** | **DMF** | **90** | **1.5** | **76** | **0** |
| 7 | 1,4-dioxane | 90 | 1.5 | 28 | <2 |
| 8 | THF | 90 | 1.5 | 20 | <2 |
| 9 | DCM | 90 | 1.5 | 26 | <2 |
| 10 | DMSO | 90 | 1.5 | 18 | <2 |
| 11 | DMF | RT | 1 | 0 | 0 |
| 12 | DMF | 60 | 1 | 27 | 0 |
| 13 | DMF | 90 | 1 | 60 | 0 |
| 14[c] | DMF | 90 | 1.5 | 32 | 0 |

[a] Reaction conditions: **4b** (1.5 mmol), **1a**, CuO Nanoparticles (20 mol %) and solvent (6 mL) were heated for 12h.[b] Isolated yields. [c] Reaction was carried out under nitrogen atmosphere.

Hence various solvents were screened to resolve this impasse (Table 4). Even though better yield of triazole was obtained under solvent free condition, it is accompanied by 21% of enaminone (Table 4, entry 4). Exclusively triazole was achieved in toluene and DMF and the enaminone was completely suppressed (Table 4, entry 5 and 6). However DMF was chosen for the OAOC of internal alkenes since it could accomplish higher yield of triazole than toluene. The temperature was also found to be pivotal to enhance the efficacy of the reaction which was confirmed from the gradual increment of yield when the temperature was raised from room temperature to 90 °C (Table 4, entry 11-13). The yield dropped apparently when the reaction was performed in degassed DMF under nitrogen atmosphere (Table 4, entry 14). This indicates that the dissolved oxygen in the solvent and the atmospheric oxygen act as the oxygen source for this transformation.

**Table 5.** Substrate Scope of Olefins and Azides[a]




| Entry | Azide | $R^1$ | $R^2$ | Olefin | Product | Yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | **1a** | H | COEt | **4a** | **5a** | 85 |
| 2 | **1a** | Ph | COPh | **4b** | **5b** | 76 |
| 3 | **1a** | 4-$BrC_6H_4$ | COPh | **4c** | **5c** | 72 |
| 4 | **1a** | 4-$ClC_6H_4$ | COPh | **4d** | **5d** | 82 |
| 5 | **1d** | Ph | COPh | **4b** | **5e** | 80 |
| 6 | **1c** | 4-$BrC_6H_4$ | COPh | **4c** | **5f** | 71 |
| 7 | **1d** | 4-$BrC_6H_4$ | COPh | **4c** | **5g** | 68 |
| 8 | **1a** | Ph | $CO_2Me$ | **4e** | **5h** | 76 |
| 9[C] | **1a** | Et | COPh | **4f** | **5i** | 65 |
| 10[C] | **1a** | Et | $COCH_3$ | **4g** | **5j** | 45 |
| 11[C] | **1a** | OBn | $CO_2Et$ | **4h** | **5k**[d] | 40 |
| 12 | **1a** | Ph | CHO | **4i** | **5l** | - |
| 13 | **1a** | Ph | $CO_2H$ | **4j** | **5m** | - |
| 14 | **1a** | H | CN | **4k** | **5n** | - |
| 15 | **1a** | H | $CO_2Et$ | **4l** | **5o** | - |

[a] Reaction conditions: olefin (1.5 mmol), Azide (2.25 mmol), CuO nanoparticles (20 mol%) and DMF (6 mL) were heated at 90 °C for 12h. [b] Isolated yields.
[C] olefin (1.5 mmol), Azide (2.25 mmol), CuO nanoparticles (20 mol%) and DMF (6 mL) were heated at 90 °C for 24h. [d] ethyl 1-benzyl-1H-1,2,3-triazole-4-carboxylate was obtained after the elimination of benzyloxy group.

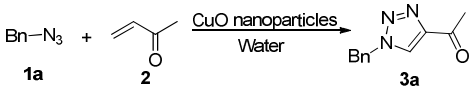
Based on the observations discussed above, OAOC of internal olefins was carried out (Table 5). In the case of chalcones, the yield has comparatively got suppressed than the terminal olefin **4a** (Table 5, entries 2-7). Moreover, aromatic substitution on the chalcones also has an impact on the efficiency of the reaction which was confirmed from the reaction of benzyl azide with chalcones **4b**, **4c** & **4d** (Table 5, entries 2-4). On the other hand, the nature of the azide was also found to be implicating the reaction since 4-methoxy benzyl azide (**1d**) furnished higher yield of triazole than benzyl azide (**1a**) when they reacted with the chalcone **4b** (Table 5, entries 2 & 5).To our delight, olefins bearing ester group such as methyl cinnamate (**4e**) also successfully worked out with good yield of the required product (Table 5, entry 8). It was found that the aliphatic substitution on the olefin significantly reduces the yield of triazoles (Table 5, entry 9-10). Push-pull olefin such as **4h** has also successfully worked out at this condition. However it has furnished 1,4-disubsitituted triazole (cycloaddition-elimination) instead of 1,4,5-trisubstituted triazole (Table 5, entry 11). At the same time, it is noteworthy that the

reaction could not work out with the olefins such as cinnamaldehyde (**4i**) and cinnamic acid (**4j**), acrylonitrile (**4k**) and ethylacrylate (Table 5, entry 12-15).

This protocol can be a potential alternative to the existing metal catalyzed azide-alkyne cycloaddition since the olefins employed here are comparatively cheaper than the alkynes and they can be synthesized easily from readily available starting materials. In the case of internal alkynes, the regioselectivity is governed by the hydrogen bond donors and electronic effects in the alkynes. [9c] On the other hand, both terminal and internal olefins employed in this method are activated ones and hence they epitomize excellent regioselectivity. Moreover, the triazoles obtained by this method from internal alkenes can render a diverse array of 1,4,5-trisubstituted 1,2,3-triazoles after further functional group manipulation on the carbonyl groups.

Finally recyclability of the heterogeneous CuO nanoparticles was also examined. The catalyst was recovered from the reaction mixture after each cycle by simple centrifugation followed by washing with ethyl acetate and dried in the hot air oven at 110 $^{o}$C for two hours. It was observed that the catalyst remains active even for four cycles (Table 6).

**Table 6.** Recycling of CuO nanoparticles




| Entry | Catalyst Recovery (%) | Cycle | Yield (%) |
|---|---|---|---|
| 1[a] | 93 | 1 | 99 |
| 2[b] | 90 | 2 | 88 |
| 3[b] | 78 | 3 | 85 |
| 4[b] | 75 | 4 | 82 |

[a] Reaction conditions: benzyl azide (3.0 mmol), methyl vinyl ketone (9.0 mmol) and water (8 mL) were stirred at room temperature for 8h. [b] The recovered catalyst was used under identical reaction conditions to those for the first run.

## Conclusions

In conclusion, we have developed an efficient protocol for the synthesis of 1,4-disubstituted and 1,4,5-trisubsitituted 1,2,3-triazoles *via* oxidative azide-olefin cycloaddition using the commercially available heterogeneous copper oxide nanoparticles under aerobic condition. A diverse array of 1,2,3-triazoles were obtained in moderate to excellent yields. All the terminal olefins worked out under ambient temperature and the time required for this transformation is comparatively less than the existing methods. Moreover, the catalyst can be recovered and reused without loss of activity and the reaction didn't necessitate any base or additives. The olefins were comparatively cheaper than the corresponding alkynes and they can be easily accessed synthetically or commercially. We hope that this method will certainly prove a boon to the needs of the scientific fraternity in academia and industries.

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Oxidative [3+2] cycloaddition of activated olefins and organic azides has been demonstrated by readily available CuO nanoparticles. A library of 1,4-disubsitituted and 1,4,5-trisubstituted 1,2,3-triazoles have been achieved without usage of base or additives in shorter reaction time. The Catalyst was recovered and reused for many cycles without loss of activity.