CLAY-SUPPORTED Cu(II) CATALYST: AN EFFICIENT, HETEROGENEOUS, AND RECYCLABLE CATALYST FOR SYNTHESIS OF 1,4-DISUBSTITUTED 1,2,3-TRIAZOLES FROM ALLOXAN-DERIVED TERMINAL ALKYNE AND SUBSTITUTED AZIDES USING CLICK CHEMISTRY

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GRAPHICAL ABSTRACT

Abstract A novel series of alloxan-derived 1,4-disubstituted 1,2,3-triazoles was synthesized in excellent yields under catalytic conditions using a click reaction strategy through 1,3-dipolar cycloaddition. Their structures have been ascertained on the basis of spectroanalytical and elemental analysis data. Synthesis of hybrid compounds with varying substitutions in the triazole ring was achieved by reaction between alloxan-derived terminal alkyne and a pertinent azide derivative in the presence of clay-Cu(II) as the catalyst in methanolic medium. Also, comparative evaluation of various catalytic systems [viz., CuI, CuSO4, CuI-zeolite, K10Ti, and clay-Cu(II)] was investigated. Of these catalytic systems, clay-Cu(II) was observed to be the best. The catalyst was recyclable for several runs without showing significant loss in its activity. The good selectivity, cost-efficiency, short reaction time, milder reaction conditions, and simple workup procedure are the added salient features of this synthetic protocol.

Keywords Alloxan; azide; catalyst; clay-copper(II); synthesis; triazoles

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INTRODUCTION

In the past few decades, research has blossomed in the synthesis of nitrogen-containing heterocyclic scaffolds, owing to their utility in diverse areas, such as pharmaceuticals, propellants, explosives, and pyrotechnics.[1] Moreover, among the vast amount of heterocyclic compounds, the triazole nuclei have been noticed as core entities in the structure of many pharmaceutically significant drugs. Therefore, their synthesis and transformations have attracted renewed interest in exploring newer synthetic protocols.[2] Specifically, the 1,2,3-triazole moiety is stable to metabolic degradation and capable of hydrogen bonding, which could be favorable in binding biomolecular targets and increasing solubility. Also, 1,2,3-triazoles can act as attractive linkers between two pharmacophores to give innovative bifunctional drugs, and thereby are useful as important complementary molecules.[3] A systematic perusal of literature reveals that this class of heterocycles is known to exhibit significant biological activities for a wide range of therapeutic ailments including antimicrobial, antitumor, anti-inflammatory, antihypertensive, analgesic, anticonvulsant, antiviral, antidepressant, antitubercular, sedative, and antioxidant activities.[4] Some of their derivatives are active constituents of currently used drugs.[5] For instance, terconazole, itraconazole, fluconazole, cefazoline, ribavirin, triazolam, alprazolam, etizolam, and furacylin are well-documented drugs embracing triazole moieties in them.[6] Obviously, the development of efficient methods for the synthesis of triazoles bearing multiple and diverse substitution patterns is highly desirable.[7] Huisgen cycloaddition reaction of dipolarophiles with 1,3-dipoles was the first set of reactions that drew the attention of synthetic organic chemists to synthesize five-membered heterocycles without the use of fancy reagents. Among various cycloaddition reactions, the azide–alkyne cycloaddition reaction was quickly identified as the most efficient approach to conjugate two or more molecules. Because the regioselectivity of this reaction is strongly controlled by steric and electronic factors, this reaction as such lacked generality and wide applicability. Later, Sharpless and coworkers set a milestone in discovering copper-catalyzed alkyne–azide cycloaddition with exceptional regioselectivity and introduced the philosophy of “click chemistry.”[8] The use of copper-catalyzed azide–alkyne cycloaddition (CuAAC) click reactions enables synthesis of macrocyclic molecules and polymers as well as modification of biomolecules, surfaces, and nanoparticles.[9,10] Benefitting from the versatility of the copper-catalyzed azide–alkyne cycloaddition (CuAAC) reactions, a range of 1,4-disubstituted-1,2,3-triazoles with adjustable electronic and steric properties has been developed for different applications including catalysis and functional molecular assemblies.[11,12] Presently, the most extensively used version of click reaction for the construction of the 1,2,3-triazole framework is the 1,3-dipolar cycloaddition reaction of azides with alkynes. As organic azides are explosive in nature,[13] comparatively unstable, and complicated to isolate, the CuAAC strategy involving in situ generation of organic azides from suitable precursors was found to be highly advantageous and safe.[14] As an effort in this direction, Guo and coworkers[15] developed such protocol using NaN₃/CuSO₄/sodium ascorbate catalytic system. However, the major limitation associated with the CuAAC protocol lies in the homogeneous nature of catalyst, thereby creating difficulty in separation. Also, the requirement of reducing agents and stabilizing ligands limits the use of this
catalyst in practical processes. Hence, to overcome these bottlenecks, we explore the heterogeneous catalytic systems that possess several advantages, such as faster and simpler isolation of the reaction products by filtration, as well as recovery and recycling of the catalysts systems.\cite{16-19} Cu(I) species immobilized onto various supports, such as silica,\cite{20} zeolites,\cite{21,22} activated charcoal,\cite{23} and clay\cite{24} have been reported recently.

Likewise, the importance of alloxan, a cyclic urea analog of chemical composition 2,4,5,6-tetraoxo-hexahydropyrimidine,\cite{34} has also been very well recognized in the literature. It is a raw material for the production of many industrial chemicals. Also on accounts of its biogenetic resemblance with uric acid it can be used to develop covalent adducts for studying diabetogenic action. Owing to the presence of $–\text{NH}$ moieties in its cyclic array, this can be explored to acts as the precursor for alkyne derivative generation. The formation of alkyne derivative is the mandatory need as the substrate material to form triazole nucleus. Prompted by these observations and in continuation of our enduring research\cite{25-30} efforts towards synthesis of novel heterocyclic compounds, it was thought worthwhile to prepare a new series of alloxan-derived triazoles (Fig. 1) using a number of catalysts as the accelerators: CuI,\cite{31} CuSO$_4$,\cite{32} CuI-zeolite,\cite{21,22} K10Ti,\cite{33} and clay-Cu(II).\cite{24} Also, the aim of the present study was to optimize the reaction conditions to observe the enhancement in the yielded outcome of the product.

**CHEMISTRY**

The synthetic protocol involved an initial bis-alkylation of alloxan 1 at N-1 and N-5 positions using propargyl bromide in the presence of K$_2$CO$_3$ in dry dimethylformamide (DMF) to yield the dipropargylated compound 2 (Scheme 1). Synthesis of precursor azide derivatives 5 (Scheme 2) was achieved as per the modified literature.

![Figure 1. Overview of triazole synthesis.](image-url)
method involving an initial C-alkylation of substituted benzene with dibromo-
methane to yield the corresponding C-alkyl bromo benzene $4$, followed by
subsequent reaction with sodium azide in presence of clay-Cu(II) catalyst in DMF
at room temperature. The desired triazole derivative $6$ was synthesized by azide–
alkyne cycloaddition reaction between pertinent precursors $2$ and $5$ in the presence
of clay-Cu(II) catalyst in a methanolic medium (Scheme 3).

After successful development of clay-Cu(II)/NaN$_3$–catalyzed protocol for
aromatic azidonation and CuAAC reaction under identical reaction conditions, we
made these two steps into a one-pot protocol for the synthesis of substituted 1,2,3
triazoles $6$. Therefore, we have opted for in situ generation of organic azide followed
by CuAAC in methanol. Obviously, this has not only prevented complicated iso-
lolation of explosive and unstable azides but also helped complete the reaction in
one pot under mild conditions. The model reaction between 4-substituted bromo
benzene $4$ (4 hydroxy bromo benzene), sodium azide, and dipropargylated alloxan
$2$ was investigated (Scheme 4). In this protocol, sodium azide, apart from its role
as an azidonation reagent, also acts as a reducing agent producing on in situ click-
active Cu(I). Structures of all the synthesized compounds were corroborated by
elemental, electrospray ionization–mass spectrometric (ESI-MS), infrared (IR),
and NMR ($^1$H, $^{13}$C) spectro-analytical findings. The clay-supported Cu(II) catalyst
was characterized using temperature programmed reduction (TPR), scanning
RESULTS AND DISCUSSION

An overview of literature reveals that several methods are available for the synthesis of 1,4-disubstituted 1,2,3-triazole and their derivatives. However, among the reported methods, many of them suffer from several bottlenecks such as poor yields, long reaction times, and harsh reaction conditions. Hence, to overcome these pitfalls and establish a convenient benign methodology, we explored the strategy of synthesizing triazoles under the prominent influence of various catalytic systems.

An initial check of the study was carried out using catalytic activity of different catalysts (5 mol% of each) such as CuI, CuSO4, CuI-zeolite, K10Ti, and clay-Cu(II) (all catalysts were either procured or prepared according to reported methods) in the condensation reaction between dipropargylated alloxan 2 (1 mmol) and benzyl azide 5 (2 mmol), in MeOH at room temperature under a nitrogen atmosphere. A close inspection of the experimental screening results reveals that when the model reaction was performed in the presence of CuI as a catalyst, the required triazole (6) was isolated in 75% yield (Table 1, entry 1). The yields of 6 have been improved slightly to 83% and 87% when the model reaction was performed in the presence of CuSO4 and CuI-zeolite, respectively, at room temperature for 5 h in MeOH (Table 1, entries

### Table 1. Effect of various catalysts in the synthesis of 6 (R=H)

| Entry | Catalyst (mol%) | Temperature | Time (h) | Yield (%) |
|-------|----------------|-------------|----------|-----------|
| 1.    | CuI            | rt          | 5        | 75        |
| 2.    | CuSO4         | rt          | 5        | 83        |
| 3.    | CuI-Zeolite   | rt          | 5        | 87        |
| 4.    | K10Ti         | rt          | 4        | 90        |
| 5.    | Clay-Cu(II)   | rt          | 4        | 96        |

Notes. Reactions were performed using di-propargylated alloxan 2 (1 mmol) and benzyl azide 5 (2 mmol), in MeOH as the solvent under nitrogen atmosphere.
2 and 3). However, when the model reaction was run in K10Ti, the reaction completed in 4 h and offered the desired triazole in 90% isolated yield (Table 1, entry 4). More interestingly, the model reaction proceeded more quickly and gave the triazole product in substantially greater yield (96%) when the reaction was performed in the presence of clay-supported Cu(II) catalyst [clay-Cu(II)] (Table 1, entry 5). Hence, though all the catalytic systems accelerated the formation of the product in appreciable yields, clay-Cu(II) was the best catalyst in terms of reaction time as well as yield of the product. The effectiveness of clay-Cu(II) catalyst may be due to the greater number of acidic sites, greater surface area, and better dispersion\(^{36,37}\) of clay platelets. Clay acts as a convenient vehicle for the chemical catalyst. Cu(II) supported by montmorillonite KSF clay resulted in further enhancement in the surface area and the total pore volume in comparison to the raw clay. The physicochemical characterization points to a successful impregnation of CuO on the clay surface (see Supplementary Data). Therefore, keeping in view the aforementioned importance associated with the catalytic system, it was our endeavor to use clay-Cu(II) catalytic system under optimized conditions owing to its large surface area and increased selectivity.

The clay-Cu(II) catalytic experiments were carried out under optimized condition from 15 min to 2 h, and products formed during the cyclization process were analyzed by GC (Table 2). The chromatogram obtained after 2 h of catalytic treatment does not contain any more substantial peak.

With these optimal conditions in hand, scope of the clay-Cu(II)–catalyzed one-pot CuAAC was investigated in a variety of solvents: toluene, tetrahydrofuran (THF), dimethylformamide (DMF), dimethylsulfoxide (DMSO), and MeOH with a view to examine their effect on reaction time and yields (Table 3). Further, upon close inspection of results, it was revealed that apolar or poorly polar solvents like toluene and THF gave no significant contribution to reaction outcome, irrespective of the temperature (Table 3, entries 1 and 2). The best yield of the cycloaddition product was obtained with polar solvents in remarkably reasonable time (Table 3, entries 3–5).

### Table 2. Effect of reaction time on product analysis

| Entry | Catalyst (mol %) | Time | Yield (%) |
|-------|-----------------|------|-----------|
| 1.    | Clay-Cu(II)     | 15 min | 10        |
| 2.    | Clay-Cu(II)     | 30 min | 30        |
| 3.    | Clay-Cu(II)     | 1.0 h  | 65        |
| 4.    | Clay-Cu(II)     | 1.5 h  | 80        |
| 5.    | Clay-Cu(II)     | 2.0 h  | 90        |

**Notes.** Reactions were performed using di-propargylated alloxan 2 (1 mmol) and benzyl azide 5 (2 mmol), in MeOH as the solvent under nitrogen atmosphere.
entries 3–5). At room temperature, DMF gave the target product in good yield (75%) (entry 3) whereas under the identical conditions, the more polar and aprotic DMSO resulted in 89% yield (entry 4). Among all the investigated solvents, polar protic solvent (i.e., methanol) was proven to be the best in this one-pot, two-step transformation, especially at 50 °C (entries 5 and 6) with reaction outcome in only 2.5 h.

Subsequent efforts were focused on optimizing conditions for the formation of 1,4-disubstituted 1,2,3-triazole using different amounts of clay-Cu(II) at varying temperatures (Table 4). Amount of catalyst was gradually reduced from 20 to 1 mol%, which resulted in the yields of 6 dropping from 98% to 97%, 95%, and 91%, respectively (Table 4, entries 1–5). Remarkably, a decrease in the amount of clay-Cu(II) from 20 to 15 mol% had only little influence on the outcome of the model reaction; the yields of 6 were nearly identical (Table 4, entry 2). More noticeably, the amount of clay-Cu(II) could be reduced sequentially up to 5 mol%, without the harsh loss in the yield (Table 4, entries 3 and 4): with only 1 mol% clay-Cu(II), the yield of 1,4-disubstituted triazole (6) was still amounted to 91% (Table 4, entry 5). To our satisfaction excellent yield of the product could be obtained even at low loading of optimal catalyst. All further reactions were run with 5 mol% of a clay-Cu(II) for investigating the effect of temperature on reaction rate as well as on percentage yields of the products. When using 5 mol% of clay-Cu(II) at 50 °C, product 6 was obtained in less time (Table 4, entry 6). Gratifyingly, when the temperature was increased to 60 °C, time was further reduced but with retained yield (Table 4, entry 7). In the absence of catalyst, the yield of product was poor (30%), suggesting the necessity of catalyst for the synthesis of 1,4-disubstituted triazole (Table 4, entry 8). Conclusively, the optimization of reaction condition revealed the use of 5 mol% of clay-Cu (II) catalyst at room temperature in methanolic medium to substantiate the product formation in 96% yield.

At the end of the reaction, the catalyst was filtered off, washed with mixture of hot ethanol and water, dried at 100 °C for 3 h, and reused as such for subsequent

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**Table 3.** Effect of various solvents in the synthesis of 6 (R=H)

| Entry | Solvent | Temperature | Time (h) | Yield (%) |
|-------|---------|-------------|----------|-----------|
| 1.    | Toluene | rt          | 20       | 35        |
| 2.    | THF     | rt          | 20       | 48        |
| 3.    | DMF     | rt          | 10       | 75        |
| 4.    | DMSO    | rt          | 07       | 89        |
| 5.    | MeOH    | rt          | 03       | 96        |
| 6.    | MeOH    | 50°C        | 2.5      | 96        |

*Notes.* Reactions were performed using di-propargylated alloxan 2 (1 mmol) and benzyl azide 5 (2 mmol), in different solvents under nitrogen atmosphere.
experiments (up to five cycles) under similar reaction conditions. Yields of the product remained comparable in these experiments (Table 5). The SEM image (see Supplementary Data) of the catalyst after use showed similar morphology and structural integrity after the fifth run, which clearly indicated that the clay-Cu(II) catalyst is robust, recyclable, and not affected under the reaction conditions of this protocol.

After developing the optimized reaction condition, the scope of this methodology was explored for the synthesis of a number of substitute triazoles. In this regard, many azides were found to elicit their feasibility to prepare the corresponding 1,4-disubstituted triazole (Table 6). Both electron-donating methyl, methoxy, and hydroxyl (compounds 6a, 6b, 6d, 6e, 6f, and 6n), and electron-withdrawing groups such as bromo, chloro, and nitro groups (compounds 6c, 6i, 6j, 6k, and 6l) gave the pertinent products in good to excellent yields. Initially, we have explored the use of 5 as the starting material with different azides for the cycloaddition reaction. Alkyl and phenyl azides gave good yields of the product: 95% (Table 6, compound 6h) and 94% (Table 6, compound 6g), respectively.

| Table 4. Influence of the amounts of clay-Cu(II) on the yields of 6\(^a\) (R=H) |
|---|
| Entry | Catalyst (mol ‰) | Temperature | Time\(^b\) (h) | Yield\(^c\) (%) |
| 1. | 20 | rt | 2 | 98 |
| 2. | 15 | rt | 2 | 97 |
| 3. | 10 | rt | 2.5 | 97 |
| 4. | 5 | rt | 3 | 96 |
| 5. | 1 | rt | 5 | 91 |
| 6. | 5 | 50 °C | 2.5 | 96 |
| 7. | 5 | 60 °C | 2 | 96 |
| 8. | No catalyst | rt to 60 °C | 20 | 30 |

\(^a\)Reactions were performed using di-propargylated alloxan 2 (1 mmol) and benzyl azide 5 (2 mmol), in MeOH solvent under nitrogen atmosphere.

\(^b\)Reactions were monitored by TLC/GC.

\(^c\)Yields are given for isolated products.

| Table 5. Recyclability of the catalyst for the synthesis of substituted 1,2,3-triazoles (6) |
|---|
| Entry | Cycle | Yield\(^d\) (%) |
| 1 | Cycle 1 | 96 |
| 2 | Cycle 2 | 93 |
| 3 | Cycle 3 | 88 |
| 4 | Cycle 4 | 84 |
| 5 | Cycle 5 | 81 |

\(^d\)Yields after consecutive cycles.
Table 6. Synthesized triazole derivatives (6a–n) from propargylated alloxan

| Compound | Benzyl azide | Product | Yield (%) |
|----------|--------------|---------|-----------|
| 6a       | 96           | 6b      | 94        |
| 6b       |              | 6c      | 94        |
| 6c       |              | 6d      | 96        |

![Chemical structures](image-url)
| Compound | Benzyl azide | Product | Yield (%) |
|----------|-------------|---------|-----------|
| 6i       | ![Structure 6i](image) | ![Structure Product 6i](image) | 93        |
| 6j       | ![Structure 6j](image) | ![Structure Product 6j](image) | 95        |
| 6k       | ![Structure 6k](image) | ![Structure Product 6k](image) | 94        |
| 6l       | ![Structure 6l](image) | ![Structure Product 6l](image) | 92        |
Note. Yield is isolated yield.
The plausible click chemistry mechanism\textsuperscript{[38]} for the formation of target compound 6 through the involvement of clay-Cu(II) catalyst via one-pot clay-Cu(II)/NaN\textsubscript{3}–catalyzed CuAAC reaction is depicted in Fig. 2. Initially, benzyl azide species A is formed by the reaction between benzyl bromide and NaN\textsubscript{3} with elimination of NaBr at the initial stage of the catalytic cycle. Now A was adsorbed on clay-Cu(II) catalyst surface and resulted in the formation of azide-catalyst conjugate B. Compound C approached the Cu-clay supported azide derivative B and resulted in the generation of triazole 6 via the intermediate species D-1 to D-3. Cyclization and tautomerism affords the corresponding products with addition of proton. XPS analysis proved that Cu(II) gets partially reduced to Cu(I) state after treatment with NaN\textsubscript{3}, and thus is present as Cu(II)/Cu(I) mixed valency dinuclear species.\textsuperscript{[39,40]}

Results were verified on the basis of XPS studies (see Supplementary Data).

CONCLUSION

In conclusion, we have developed a simple, economically viable, safe, and highly efficient one-step regiospecific synthesis of biologically important 1,4-disubstituted
1,2,3-triazoles via Huisgen 1,3-dipolar cycloaddition reaction of terminal alkynes, alloxan, and azide in the presence of clay-Cu(II) as the catalyst using MeOH as reaction medium. Also, we have investigated the influence of various catalysts on the alloxan-derived 1,4-disubstituted triazole synthesis. Among them, clay-Cu(II) was established as the best catalyst in terms of reaction time and yield of the product. Clay-Cu(II) is therefore regarded as the ligand-free, leaching-free, easy to prepare, easy to handle, and environmentally benign catalytic system. All these features make it highly useful for economical synthesis of 1,4-disubstituted 1,2,3-triazoles. A clean and efficient reaction, simple workup of the product, and extensive applicability of the strategy to a variety of substrates make this method of high practical utility.

**EXPERIMENTAL**

All the chemicals used in the synthesis were of analytical reagent grade purity (Sigma-Aldrich) and were used as such without further purification. Column chromatography, thin-layer chromatography (TLC), and gas–liquid chromatography (Agilent 7820A, equipped with Flame Ionization Detector) were used to monitor the progress of the reaction as and where needed. Melting points were determined by open capillary using Veego precision digital melting-point apparatus (MP-D) and are uncorrected. IR spectra were recorded on a Shimadzu D-8001 spectrophotometer. The $^1$H and $^{13}$C NMR spectra of the synthesized compounds were recorded at 400 and 100 MHz, respectively, using Bruker Avance 400-MHz NMR spectrometer in DMSO-d$_6$ solvent. The chemical shifts were expressed in $\delta$ relative to tetramethylsilane (TMS) as internal standard and coupling constants ($J$) are given in hertz (Hz). Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; m, multiplet; dd, double doublet; ddd, doublet of a doublet of a doublet; and br, broad peak. Mass spectra were recorded on Shimadzu GCMS-QP-2000 mass spectrometer. Column chromatography was performed on silica gel (60–120 mesh). Reducible character of the catalyst was determined by chembet-3000 TPR instrument. XPS spectra were recorded by VG ESCA LAB MK II spectrometer using Al K\(\alpha\) (1486.6 eV) radiation from an x-ray source operated at 12 kV, 10 mA. Scanning electron microscopy (SEM) measurements were obtained by on a Jeol JSM 5600 instrument. SEM (EDAX) elemental analysis was carried out to find out the percentage of Cu in clay-Cu(II) catalyst, which was observed to be 7.93% in the form of aggregates of CuO particles in the catalyst.

**Typical Procedure for the Synthesis of 1,5-Dipropargylated Alloxan (2)**

Alloxan (1 mmol) was added to a well-stirred suspension of potassium carbonate (4 mmol) in dry DMF. The resulting suspension was stirred for 15 min at room temperature followed by the addition of propargyl bromide (2.2 mmol). The contents were stirred at room temperature for 6–7 h. The GC analysis showed nearly 85% yield. Later the product mixture was treated with brine solution and extracted with (2 × 50 mL) ethyl acetate. The organic layer were combined, dried over anhydrous sodium sulfate (Na$_2$SO$_4$), and concentrated under reduced pressure. The crude
Typical Procedure for the Synthesis of Substituted N-Alkyl Bromo Benzene (4)

Benzene (1 mmol) was added to a stirred suspension of sodium hydride (1.5 mmol) in dry DMF (10 mL). The solution was stirred at room temperature until the evolution of hydrogen ceased. To this reaction mixture, a solution of dibromo-methane (1.1 mmol) in DMF was added dropwise. The reaction mixture was heated to 60°C with constant stirring for about 2 h. The GC analysis shows around 72% yield and the products were purified with the help of column chromatography using hexane–ethyl acetate (8:2 v/v) mixture.

Typical Procedure for the Synthesis of Substituted N-Alkyl Azido Benzene (5)

NaN₃ (1.5 mmol) and clay-supported Cu catalyst (5 mol%) were added to the stirred suspension of N-alkyl bromo benzene in dry DMF, and the reaction mixture was heated at 60°C for about 3 h (monitored by TLC/GC). When around 85% conversion occurred, the reaction mixture was extracted with ethyl acetate and the organic layer was washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to yield N-alkyl azido benzene derivatives in good yields.

Typical Procedure for the Synthesis of Alloxane–Benzene Conjugates (6)

Clay-supported copper catalyst [clay-Cu(II)] (5 mol%) at room temperature was added to the stirred solution of 2 (1 mmol) and 5 (2 mmol) in methanol, in succession. The completion of reaction was monitored by TLC/GC. The reaction mixture was filtered through Whatman filter paper and the residue was washed with ethyl acetate. The remaining solid (recovered catalyst) was washed with ethanol and water, dried (at 100°C for 3 h), and reused (for the recyclability experiment). Filtrate was extracted with ethyl acetate (2×50 mL) and dried over anhydrous sodium sulfate. The combined organic layer was concentrated in vacuo and crude reaction mixture was purified by silica gel (100–200) column chromatography using ethyl acetate–hexane (3:7 v/v) as eluting solvent to get corresponding 1,4-disubstituted 1,2,3-triazoles 6a–n in 92–96% yield.

Typical Procedure for One-Pot Synthesis of 1,4-Disubstituted 1,2,3-Triazole (6)

N-Alkyl bromo benzene (4, 1 mmol) and sodium azide (2 mmol) were stirred in methanol–water (10:1) for 10 min. Clay-supported Cu catalyst (5 mol%) was then added and the reaction mixture was stirred for another 30 min. The in situ formation of N-alkyl azido benzene was monitored by TLC. The 1,5-dipropargylated alloxan product was purified with column chromatography using a (65:35 v/v) mixture of hexane–ethyl acetate to yield the desired precursor 2.
(2, 1 mmol) was added and reaction mixture was stirred at room temperature for 3 h. The completion of reaction was monitored by TLC. The reaction mixture was filtered through Whatman filter paper and residue was washed with ethyl acetate. Remaining solid (recovered catalyst) was washed with ethanol and water, dried (at 100 °C for 3 h), and reused (in the recyclability experiment). Filtrate was extracted with ethyl acetate (2 × 50 mL) and dried over anhydrous sodium sulfate. Combined organic layer was concentrated in vacuo and crude reaction mixture was purified by silica gel (100–200) column chromatography using ethyl acetate–hexane (3:7 v/v) as eluting solvent to get corresponding 1,4-disubstituted 1,2,3-triazoles 6a–n in 92–96% yield.

1,3-Bis((1-(4-hydroxybenzyl)-1H-1,2,3-triazole-4-yl)methyl) pyrimidine-2,4,5,6(1H,3H)-tetraone (6a)

Green solid, yield 96%; mp 188–190 °C; IR (KBr, ν, cm⁻¹); 3440, 3064, 2921, 2806, 1726, 1630, 1609, 1470, 1132, 1024. ¹H NMR (400 MHz, DMSO-d₆): δ: 4.65 (s, 4H, 2 × CH₂), 4.97 (s, 4H, 2 × CH₂), 5.56 (s, 2H, OH), 7.05 (d, 4H, J = 8.0 Hz, Ar-H), 7.32 (d, 4H, J = 8.0 Hz, Ar-H), 8.1 (s, 2H, triazole-H). ¹³C NMR (100 MHz, DMSO-d₆): δ: 47.7, 56.8, 116.3, 122.5, 125.3, 127.9, 128.7, 129.9, 130.5, 131.8, 150.4, 155.1, 158.3, 173.3. ESI–MS: 516 [M+H]⁺. Anal. calcd. for C₂₄H₂₀N₈O₆: C, 55.81; H, 3.90; N, 21.70%. Found: C, 55.96; H, 4.05; N, 21.56%.

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SUPPLEMENTAL MATERIAL

Spectra of catalyst, full experimental details, and ¹H NMR, ¹³C NMR data for this article can be accessed on the publisher’s website.

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