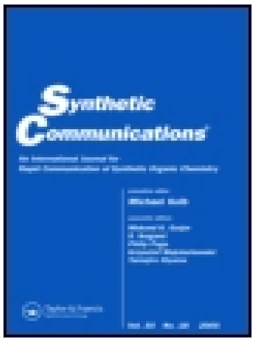

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Clay Supported Cu(II) catalyst: An Efficient, Heterogeneous, and Recyclable Catalyst for Synthesis of 1,4-disubstituted 1,2,3-triazoles from Alloxan-Derived Terminal Alkyne and Substituted Azides using click Chemistry Approach

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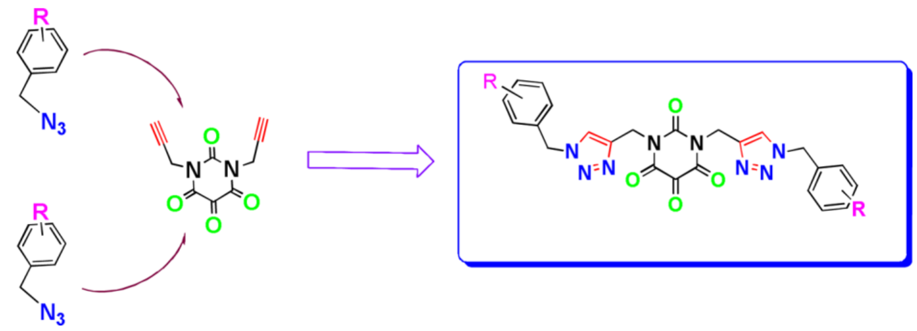
Abstract

A novel series of alloxan embraced 1,4-disubstituted 1,2,3-triazoles was synthesized in excellent yields under catalytic conditions using click reaction strategy through 1,3-dipolar cycloaddition. Their structures have been ascertained on the basis of spectroanalytical and elemental analyses data. Synthesis of hybrid compounds with varying substitution 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, $CuSO_4$, CuI-zeolite, K10Ti and clay-Cu(II) was investigated. However, out of these catalytic systems, clay-Cu(II) was observed to be the best amongst all. 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 work-up procedure are the added salient features of this synthetic protocol.



KEYWORDS: Synthesis, Triazoles, Alloxan, Azide, Catalyst, Clay-Copper(II)

INTRODUCTION

A tremendous growth of research has blossomed in the last few decades in the synthesis of nitrogen containing heterocyclic scaffolds owing to their utility in diversified areas viz., as pharmaceuticals, propellants, explosives and pyrotechnics.[1] Moreover, amongst a vast majority of heterocyclic compounds, the triazole nuclei have been noticed as the core entity in the structural armamentarium of many pharmaceutically significant drugs. Therefore, its synthesis and transformations have attracted renewed interest of researchers towards exploration of newer synthetic protocols.[2] Specifically, 1,2,3-triazole moiety is stable to metabolic degradation and capable of hydrogen bonding, which could be favorable in binding of biomolecular targets and increasing solubility. Also, 1,2,3-triazoles can act as attractive linker between two pharmacophores to give innovative bifunctional drugs, and thereby useful as an important complimentary molecule.[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 viz., 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, Ribavarin, Triazolam, Alprazolam, Etizolam and Furacylin are the well documented drugs embracing triazole moiety in them.[6] Obviously, interest in 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 including triazoles 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. Since 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 co-workers 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 have 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, copper azide-alkyne cycloaddition (CuAAC) strategy involving *in situ* generation of organic azides from suitable precursors was found to be highly advantageous and safe.[14] As an effort toward this aspect, Guo and coworkers[15] developed such protocol using $NaN_3/CuSO_4$/sodium ascorbate catalytic system. However, the major limitation associated with CuAAC protocol lies in the homogeneous nature of catalyst, and thereby creating a difficulty in its separation. Also, the requirement of reducing agents and stabilizing ligands poses the limited use of this catalyst in practical processes. Hence, keeping this in view and to overcome these bottlenecks, it was our endower to explore the heterogeneous catalytic systems which posses several advantages, such as faster and simpler isolation of the reaction products by filtration, as well as recovery and recycling of the catalysts systems.[16-19] Cu(I) species immobilized onto various supports, such as silica,[20] zeolites,[21,22] activated charcoal,[23] and clay[24] have been reported recently.

Likewise, the importance of alloxan, a cyclic urea analogue of chemical composition 2,4,5,6-tetraoxo-hexa hydropyrimidine[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 –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[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 viz; CuI,[31] $CuSO_4$,[32] CuI-zeolite,[21,22] K10Ti[33] and clay-Cu(II).[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

Synthetic 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_2CO_3 in dry DMF to yield the di-propargylated compound **2** (scheme 1). Synthesis of precursor azide derivatives **5** (scheme 2) was achieved as per the modified literature method[35] involving an initial C-alkylation of substituted benzene with dibromomethane 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 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 paid our attention to renovate these two steps into one-pot protocol for the synthesis of substituted 1,2,3 triazoles **6**. Therefore, we have opted an in situ generation of organic azide followed by CuAAC in methanol. Obviously, this has not only prevented complicated isolation of explosive and unstable azides but also helped in carrying out completing reaction in one pot under mild conditions. The model reaction between 4-substituted bromo benzene **4** (4 hydroxy bromo benzene), sodium azide and di-propargylated 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, ESI-MS, IR and NMR (^{1}H, ^{13}C) spectro-analytical findings. The clay-supported Cu(II) catalyst was characterized using temperature programmed reduction (TPR), scanning electron microscope (SEM) experiment and X-ray photoelectron spectra (XPS) analysis/studies (see Supplementary data).

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, amongst the reported methods, many of them suffer from several bottlenecks such as the low yield, longer reaction time, and harsh reaction conditions. Hence, in view to overcome all these pitfalls and to establish a convenient benign methodology, we have 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, $CuSO_4$, Cu^I-zeolite, K10Ti and clay-Cu(II) (all catalysts were either procured or prepared according to reported methods) in the condensation reaction between di-propargylated alloxan **2** (1 mmol) and benzyl azide **5** (2 mmol), in MeOH at room temperature under 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 yield of **6** has been improved slightly to 83% and 87%, respectively, when the model reaction was performed in the presence of $CuSO_4$ and Cu^I-zeolite, respectively at room temperature for 5 h in MeOH (Table 1, entries 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, model reaction proceeded very faster and gave the triazole product in substantially higher yield (96%), when the reaction was performed in the presence of clay supported Cu (II) catalyst [clay-Cu(II)] (Table 1, entry 5). Hence, the basis of these results, it was observed that, though all the catalytic systems accelerated the formation of the product in appreciable yields, however clay-Cu(II) was proven to be the best catalyst in terms of reaction time as well as obtained yield of the product. The effectiveness of clay-Cu(II) catalyst may be due to the more number of acidic sites, higher 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 caparison 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 copper azide-alkyne cycloaddition reaction (CuAAC) was investigated in variety of solvents viz., toluene, THF, DMF, 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 on 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). 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 hour.

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 mol % to 1 mol %, which was resulted in the yields of **6** dropped 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 fewer time (Table 4, entry 6). Gratifyingly, when the temperature was increased to 60 ^{0}C, time was further reduced but with retained yield (Table 4, entries 7). In the absence of catalyst, the yield of product was very much feeble (30%), hereby suggesting the necessity of catalyst for the synthesis of 1,4-disubsituted 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 ^{0}C for 3 h, and reused as such for subsequent experiments (up to five cycles) under similar reaction conditions. It was noticed that 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 5th run, which clearly indicated that the clay-Cu(II) catalyst is robust, recyclable, and was 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, hydroxyl (compounds 6a, 6b, 6d, 6e, 6f and 6n), and electron withdrawing groups such as bromo, chloro, 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 viz; 95% (Table 6, compound 6h) and 94% (Table 6, compound 6g), respectively.

The plausible click chemistry mechanism[38] for the formation of target compound **6** through the involvement of clay-Cu(II) catalyst *via* one-pot clay-Cu(II)/NaN_3 catalyzed CuAAC reaction is depicted in the Fig. 2. Initially, benzyl azide species **A** is formed by the reaction between benzyl bromide and NaN_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_3, and thus is present as Cu(II)/ Cu(I) mixed valency dinuclear species.[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 between 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. Amongst them, clay-Cu(II) was establised to be the best catalyst in terms of reaction time as well as yield of the product. Clay-Cu(II) is therefore, regarded as the ligand-free, leaching-free, easy to prepare, easy to handle, 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 work-up of the product and extensive applicability of the strategy to a variety of substrates render this method to be of high practical utility.

EXPERIMENTAL SECTION

All the chemicals used in the synthesis were of AR grade purity (Sigma-Aldrich) and were used as such without further purification. Column chromatography/ Thin layer chromatography/ Gas Liquid Chromatograph (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 MHz and 100 MHz, respectively using Bruker AVANCE 400 MHz NMR spectrometer in DMSO-d_6 solvent and the chemical shifts were expressed in δ relative to TMS as internal standard and coupling constants (*J*) in Hz. Chemical shift values are expressed as parts per million down field from TMS and J values are in hertz. 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 a silica gel (60-120 mesh). Reducible character of the catalyst was determined by chembet-3000 TPR instrument. XPS spectra was recorded by VG ESCA LAB MK II spectrometer using Al Kα (1486.6 eV) radiation from an X-ray source operated at 12 kV, 10mA. Scanning electron microscopy (SEM) measurements were obtained by JEOL JSM 5600. SEM (EDAX) elemental analysis was carried out to find out the percent 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)

To a well stirred suspension of potassium carbonate (4 mmol) in dry DMF alloxan (1 mmol) was added. 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. GC analysis shows nearly 85% yield. Later on 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_2SO_4) and concentrated under reduced pressure. The crude product was purified with column chromatography using a (65:35 v/v) mixture of hexane: ethyl acetate to yield the desired precursor **2**.

Typical Procedure For The Synthesis Of Substituted N-Alkyl Bromo Benzene (4)

To a stirred suspension of sodium hydride (1.5 mmol) in dry DMF (10 mL) benzene (1 mmol) was added. The solution was stirred at room temperature till the evolution of hydrogen ceases. To this reaction mixture, a solution of dibromomethane (1.1 mmol) in DMF was added drop wise. The reaction mixture was heated to 60 °C with constant stirring for about 2 h. 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)

To the stirred suspension of N-alkyl bromo benzene in dry DMF, NaN_3 (1.5 mmol) and clay supported Cu catalyst (5 mol %) was added and the reaction mixture was heated at 60 ^{0}C for about 3 h (monitored by TLC/GC). When around 85% conversion occur , the reaction mixture was extracted with ethyl acetate and the organic layer was washed with brine, dried over anhydrous Na_2SO_4 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)

To the stirred solution of **2** (1 mmol) and **5** (2 mmol) in methanol, clay supported copper catalyst [clay-Cu(II)] (5 mol %) at room temperature was added in succession. The completion of reaction was monitored by TLC/ GC. 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 case of 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.

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

N-alkyl bromo benzene (**4**, 1mmol) and sodium azide (2 mmol) were stirred in methanol-water (10:1) for 10 minute. Clay supported Cu catalyst (5 mol %) was then added and reaction mixture was stirred for another 30 minute. The in situ formation of N-alkyl azido benzene was monitored by TLC. The 1,5-dipropargylated alloxan (**2**, 1 mmol) was added and reaction mixture was stirred at room temperature for 3 hours. 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 case of 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%; m.p.188-190 °C; IR (KBr, ν, cm^{-1}); 3440, 3064, 2921, 2806, 1726, 1630, 1609, 1470, 1132, 1024. ^1H NMR (400 MHz, DMSO-d_6) δ: 4.65 (s, 4H, $2\times CH_2$), 4.97 (s, 4H, $2\times CH_2$), 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). ^{13}C NMR (100 MHz, DMSO-d_6) 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 $C_{24}H_{20}N_8O_6$: 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 and full experimental details, ^1H NMR, ^{13}C NMR data and spectra for this article can be accessed on the publisher’s website.

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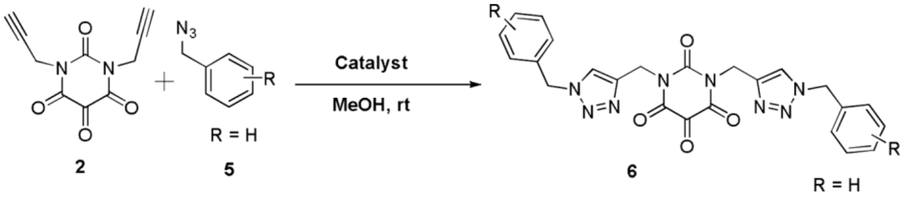
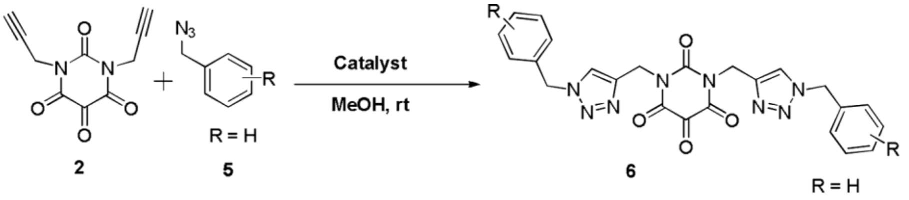
Table 1. Effect of various catalysts in the synthesis of **6**[*] (R = H)



Entry	Catalyst (mol %)	Temperature	Time (h)	Yield (%)
1	CuI	rt	5	75
2	$CuSO_4$	rt	5	83
3	Cu^I-Zeolite	rt	5	87
4	K10Ti	rt	4	90
5	Clay-Cu(II)	rt	4	96

[*] Reactions were performed using di-propargylated alloxan **2** (1 mmol) and benzyl azide **5** (2 mmol), in MeOH as the solvent under nitrogen atmosphere

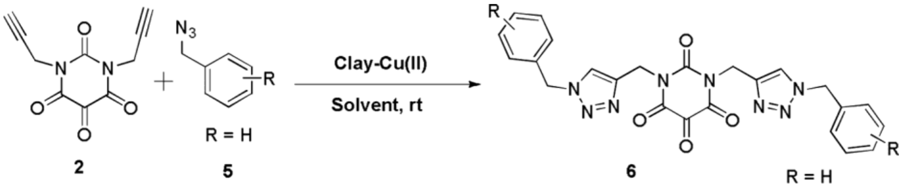
Table 2. Effect of reaction time on product analysis*



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 hour	65
4	Clay-Cu(II)	1.5 hour	80
5	Clay-Cu(II)	2.0 hour	90

*Reactions were performed using di-propargylated alloxan **2** (1 mmol) and benzyl azide **5** (2 mmol), in MeOH as the solvent under nitrogen atmosphere

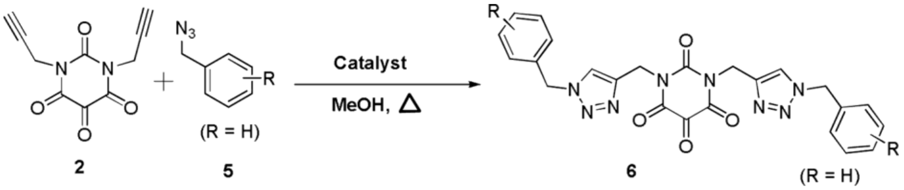
Table 3. Effect of various solvents in the synthesis of **6*** (R = H)



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

*Reactions were performed using di-propargylated alloxan **2** (1 mmol) and benzyl azide **5** (2 mmol), in different solvent under nitrogen atmosphere

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

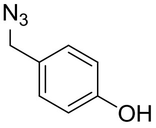
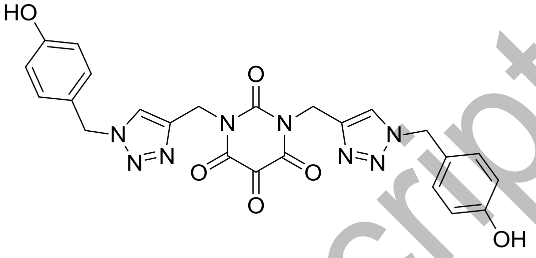
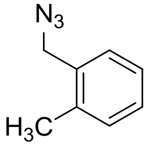
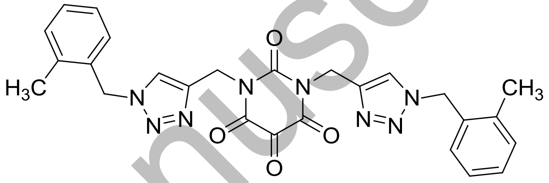
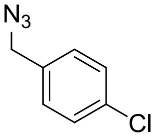
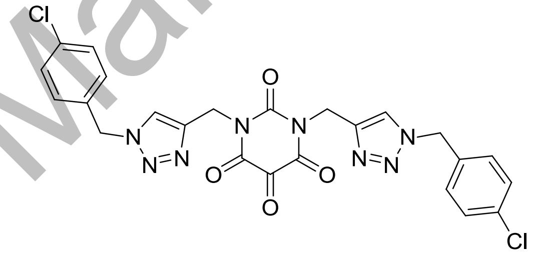
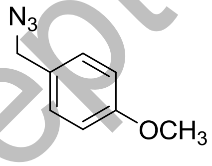
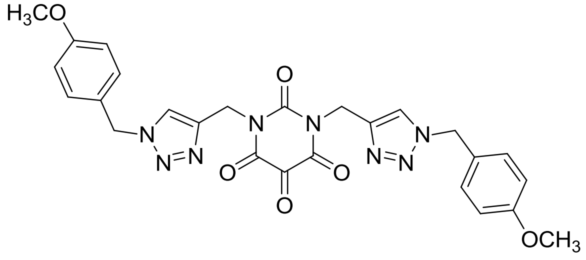
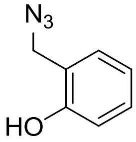
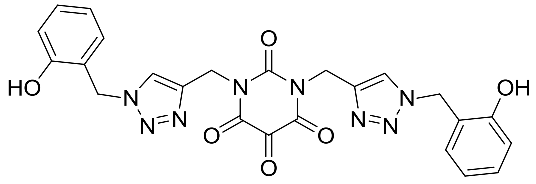
[c] Yields are given for isolated products

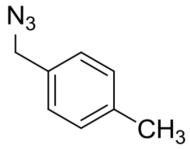
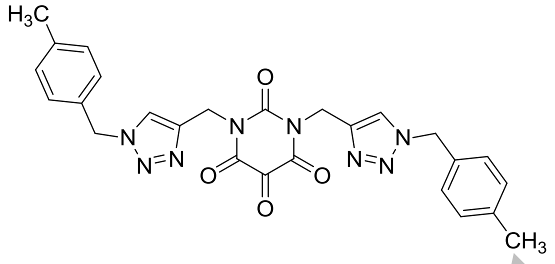
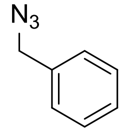
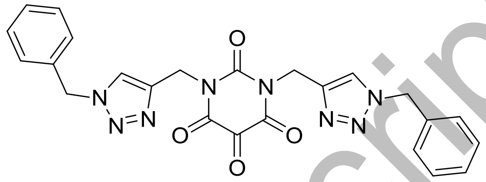
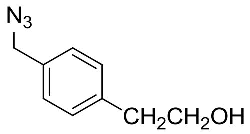
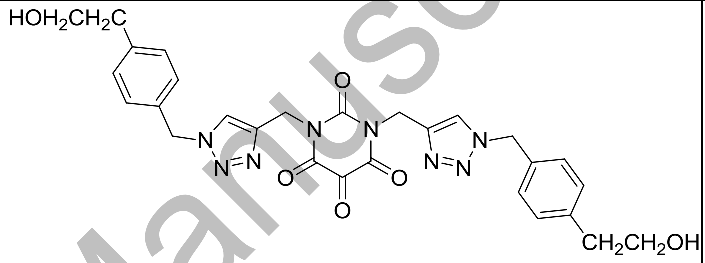
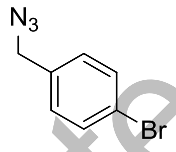
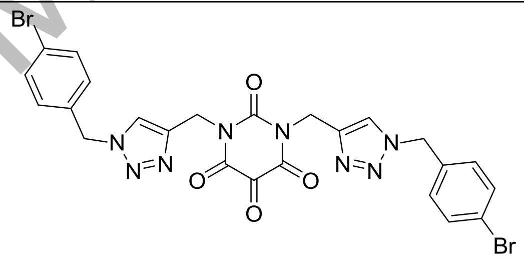
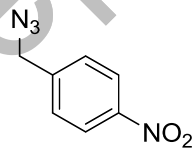
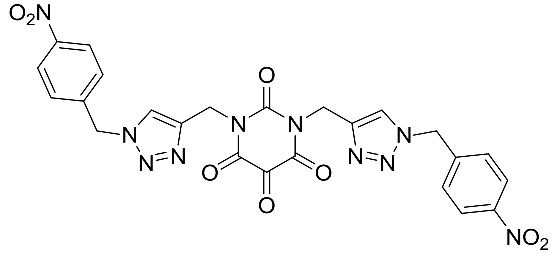
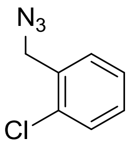
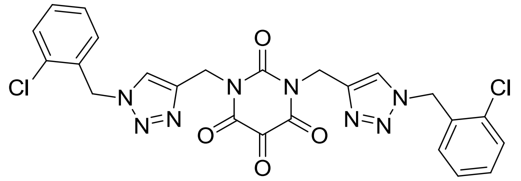
Table 5. Recyclability of the catalyst for the synthesis of substituted 1,2,3 triazoles (**6**)

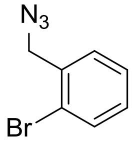
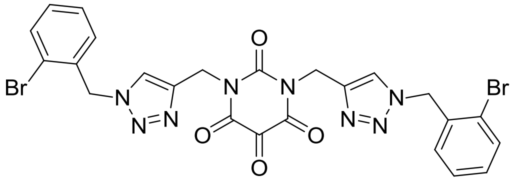
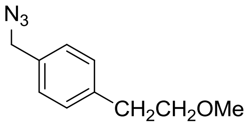
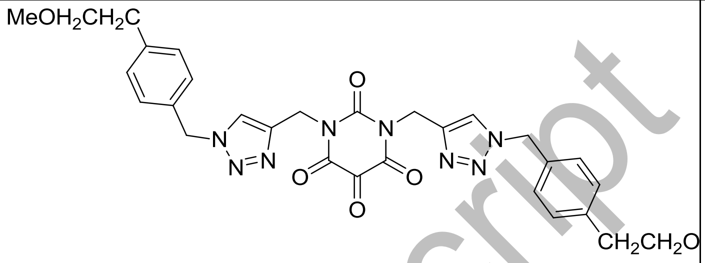
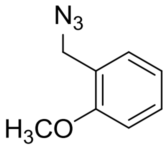
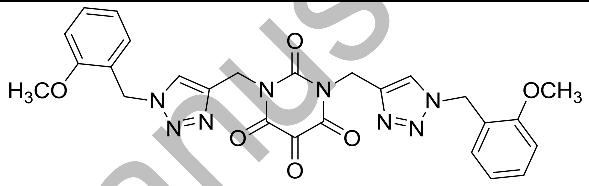
Entry	**Cycle**	**Yield[a] (%)**
1	Cycle 1	96
2	Cycle 2	93
3	Cycle 3	88
4	Cycle 4	84
5	Cycle 5	81

[a] Yields after consecutive cycles.

Table 6. Synthesized triazole derivatives (6**a-n**) from propargylated alloxan

Compound number	**Benzyl azide**	**Product**	**Yield (%)***
6a			96
6b			94
6c			94
6d			96
6e			95

6f			95
6g			94
6h			95
6i			93
6j			95
6k			94

6l			92
6m			95
6n			96

* Isolated yield

Figure 1.Overview of triazole synthesis

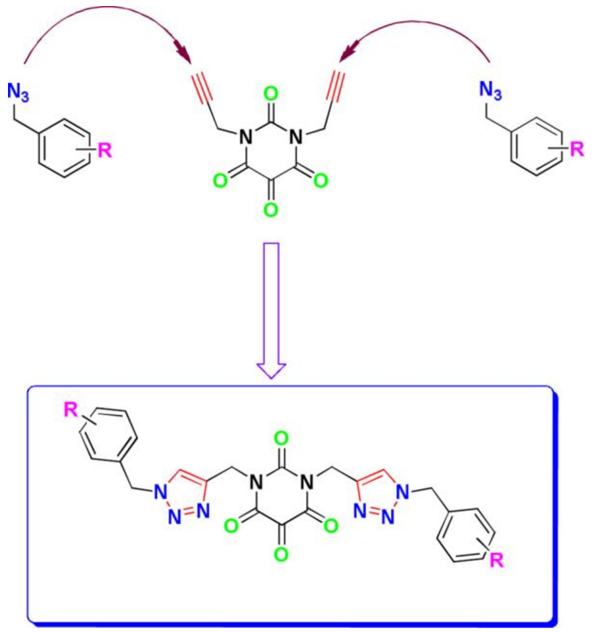
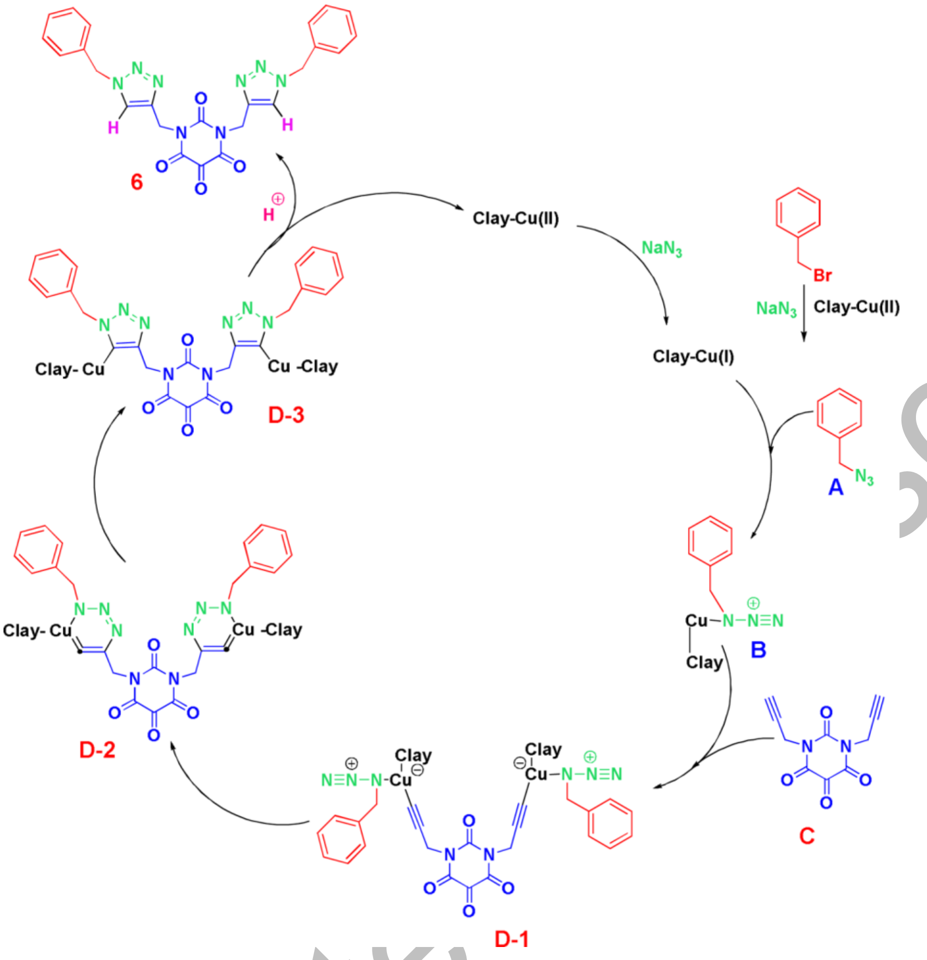
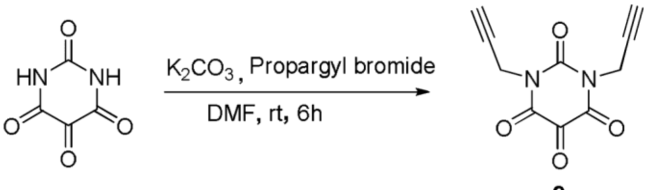


Figure 2. Plausible mechanism of one-pot CuAAC protocol using clay-Cu(II) catalyst



Scheme 1. Synthesis of 1,5-dipropargylated alloxan



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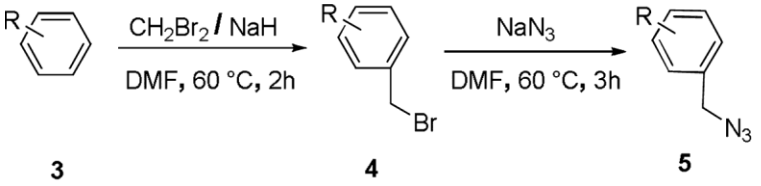
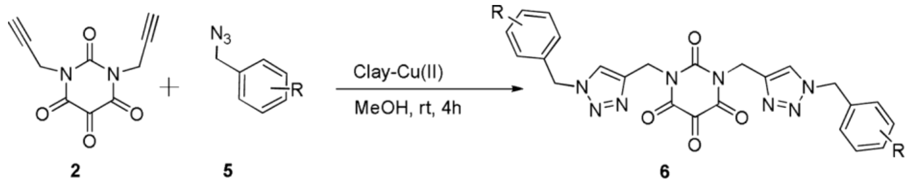
Scheme 2. Synthesis of substituted benzyl azides



R = H, OH, CH_3, OCH_3, Cl, Br, NO_2, etc

Scheme 3. Synthesis of substituted 1,2,3-triazoles via alloxan-benzyl azide-conjugates through click chemistry



Scheme 4. One-pot click chemistry approach for the synthesis of substituted 1,2,3-triazole using clay·Cu(II)/NaN$_3$·catalysed CuAAC reaction