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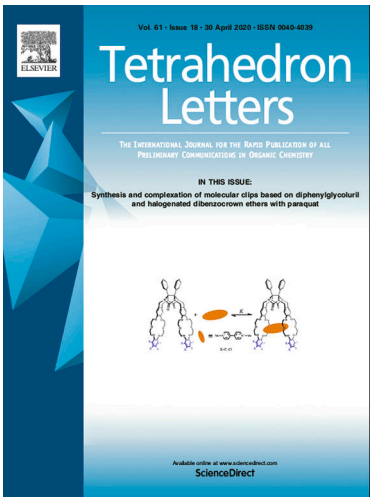

Sequencing [3 + 2]-Cycloaddition and Multicomponent Reactions: A Regioselective Microwave-assisted Synthesis of 1,4-Disubstituted 1,2,3-Triazoles using Ionic Liquid Supported Cu(II) Precatalysts in Methanol

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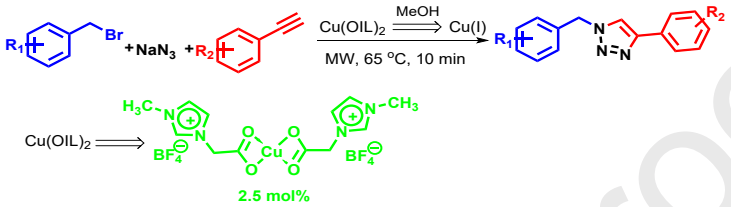

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ABSTRACT

Heterocyclic compounds with two to three nitrogen atoms play a pivotal role in the normal life cycle of a cell. Further the design and synthesis of a quality heterocyclic compound library with N-atoms as new chemical probes active, is vital in drug discovery. In this context, an efficient one-pot multicomponent strategy for the synthesis of a mini library of 1,4-disubstituted 1,2,3-triazoles is described. This new multicomponent one-pot method features a combination of ionic liquid supported Cu(II) precatalysts in methanol catalyzed [3 + 2]-cycloaddition with microwave irradiation reactions. The synthetic manipulation involved the efficient reduction of ionic liquid supported Cu(II) catalyst by methanol followed by [3 + 2] cycloaddition with alkynes using in situ generated azides to obtain 1,2,3-triazoles regioselectively..

1. Introduction

To sustain drug discovery campaigns, the diversity oriented synthesis (DOS) has become an indispensible tool for the synthesis of nature-inspired and drug like small molecule.[1] Similarly, multicomponent reactions, one of the key aspects of DOS, allow the formation of multiple bonds at a time using more than two reactants in a single step.[2] The discovery of highly regioselective Cu(I) catalysed (3+2) cycloadditions in 2001 by Sharpless and his co-workers rapidly gained an important ground in all branches of chemistry including material sciences also.[3] The Cu(I) catalyzed (3+2) cycloaddition is the most widely studied reaction among all Cu-catalyzed reactions.[4] The end product 1,4-disubstituted 1,2,3-triazole is a biologically valuable frameworks that are found in a large number of natural products and pharmaceutically active compounds.[5] Further, 1,4-Disubstituted 1,2,3-triazole derivatives exhibited several biological activities such as antiviral, anticancer, anti-inflammatory, and antibacterial activity.[6] The core structure of disubstituted triazoles has also been found in many drugs such as ribavitrin (A), tazobactam (B), and triazole containing naamine A and isonaamine A mimics (C, D) as shown in figure 1.[7]

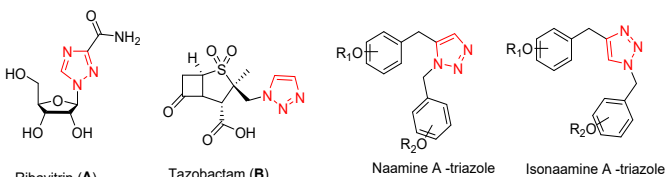

Figure 1. Biologically active triazole moieties.

In view of their wide ranging bioactivities, several synthetic methods have been developed for the 1,3-dipolar cycloaddition to 1,2,3-triazole moieties which mainly consists of Cu(II) salts with sodium ascorbate as reducing agent or Cu(I) salts.[8] Similarly Cu(I) based heterogeneous catalysts also used such as copper nanocluster,[9] copper(I) zeolites,[10] a copper manganese spinel oxide,[11] Cu/C,[12] and Cu_2O on water.[13] Further, we have demonstrated the facet dependent catalytic potential of Cu_2O nanocrystals for the regioselective synthesis of focused 1,4-disubstituted 1,2,3-triazoles in green media.[14] Lautens and his group reported the intramolecular Cu(I)-catalyzed interrupted click–acylation domino reaction.[15] In 2016, Lal et al. reviewed the use of copper nanoparticles as catalyst for the synthesis of 1,4-disubstituted 1,2,3-triazoles in water.[16] Zhu and his coworkers recently studied the use of $Cu(OAc)_2$ as catalyst for 1,3-dipolar cycloaddition reactions with particular emphasize on chelating ligands.[17] More recently, the use of Cu(II)-tren precatalysts and Cu(II)acetate precatalysts in methanol for the 1,3-dipolar cycloaddition reactions to afford the desired 1,2,3-triazole evoked the special interest for Cu(II) catalysts.[18] In spite of these tremendous achievements in this field, still there is a scope for the development of better reaction methodology in terms of single step reactions, recyclable catalysts, atom economy, and avoid the handling of explosive azides etc.

Task specific ionic liquids (TSILs) with functional groups anchored to the either cation, or anion has been developed for numerous organic transformation.[19] To suite organic transformations, many low molecular weight TSILs have been used either as supported catalysts, reagents, or as soluble supports.[20] The whole property of an ionic liquid such as thermal stability, vapor pressure, and the solvating ability can be altered by fine tuning the types of cations and anions. Advantages' lying with ionic liquid supported catalysts is the ability to easily phase separate from the substrate and products after completion of the reaction simply by adding a less polar organic solvent. Finally, the recovered ionic liquid supported catalyst can be regenerated or reused for further organic transformation. Recently, ionic

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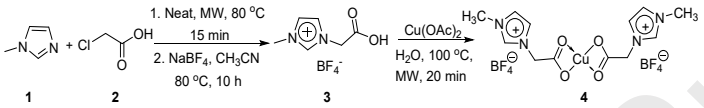
heterogeneous catalysts to promote the sustainable development in organic synthesis. In past, we have demonstrated the synthesis of unique heterocyclic scaffolds using task specific ionic liquids (TSILs) as soluble support under microwave heating.[21] The use of microwave (MW) technology in chemical synthesis is greatly established which offers simple, clean, fast, efficient, and economic features for the synthesis of a large number of organic molecules compared to the conventional heating system.[22] The use of microwaves greatly reduced the reaction time in minutes compared to hours in conventional heating conditions. As part of our ongoing programme on the diversity-oriented synthesis of bioactive heterocycles,[23] we to report herein, a regioselective microwave-assisted synthesis of 1,4-disubstituted 1,2,3-triazoles using ionic liquid supported Cu(II) precatalysts in methanol by sequencing 1,3-dipolar cycloaddition and multicomponent reactions. The synthetic manipulation involves the reduction of ionic liquid supported Cu(II) catalyst in methanol followed by microwave-assisted 1,3-dipolar cycloaddition of *in situ* generated organic azide with alkynes in excellent yields.

2. Results and Discussion

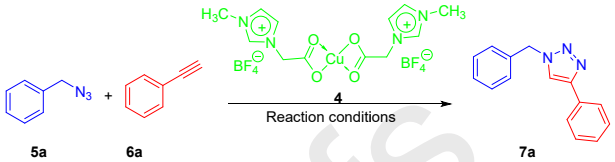
At the onset of our study, the recyclable ionic liquid supported copper (II) catalyst **4** was synthesized in aqueous solutions in three steps starting from 1-methyl imidazole **1** and 2-chloro acetic acid **2** as depicted in scheme 1 using microwave irradiation.



Scheme 1. Three step synthesis of ionic liquid supported Cu(II) catalyst **4** in aqueous medium

The synthetic strategy towards the synthesis of ionic liquid support **3** equipped with carboxyl group linker, 1-(1-carboxymethyl)-3-methylimidazolium tetrafluoroborate ([Carbmmim][BF_4]) was prepared in two steps under microwave irradiation. The first step involved the reaction of N-methyl imidazole **1** with 2-chloroacetic acid **2** in neat condition under microwave irradiation at 80 °C for 15 minutes followed by anion exchange reaction with $NaBF_4$ resulted the ionic liquid support **3**. Subsequently, the next step involved the reaction of ionic liquid support **3** with $Cu(OAc)_2$ in water medium under microwave irradiation for 20 min to obtain the ionic liquid supported copper (II) catalyst **4** as light blue powder in 95% yield. The catalyst **4** was subsequently characterized by ^1H, ^{13}C NMR, MS, IR and atomic absorption spectroscopic measurement with an attached ionic liquid (IL-tag). The quantitative catalyst formation was depicted in each step on ionic liquid support (See supporting information). As a model reaction, we attempted the reaction of benzyl azide **5a** with phenyl acetylene **6a** in the presence of ionic liquid supported Cu(II) catalyst **4**. To optimize the conditions, the above reaction was performed using a 2.5 mol% of ionic liquid supported Cu(II) catalyst **4** without using any solvent at 80 °C for 4 hours. No desired triazole product **7a** was obtained under this reaction condition (Table 1, entry 1). The reaction was further tried in polar aprotic solvents such as CH_3CN and DMSO. In both cases, no required product was obtained (Table 1, entry, 2, 3). Therefore, the reaction was further conducted in refluxing EtOH solvent. Interestingly, the product **7a** was obtained in moderate yield (45%, Table 1, entry 4). Inspired by this result, we tested the efficacy of this cycloaddition reaction with solvent such as H_2O-IPA (Table 1, entry 5) which failed to increase the yield to an appreciable extent. Even the use of H_2O as solvent Subsequently, we tried with MeOH as solvent at refluxing temperature for 4 hours which dramatically increases the reaction yield upto 80% (Table 1, entry 7). The above results indicate that the MeOH is the most effective solvent for this cycloaddition reaction.

Table 1. Optimization of 1,3-dipolar cycloaddition reaction between benzyl azide and phenyl acetylene catalyzed by ionic liquid supported Cu(II) catalyst **4**.[a]



entry	solvent	temperature	time	Yield%[c]
1	Neat	80 °C	4h	0%
2	CH_3CN	reflux	4 h	0%
3	DMSO	80 °C	4 h	0%
4	EtOH	reflux	4 h	45%
5	H_2O-IPA	80°C	4 h	40%
6	H_2O	reflux	4 h	35%
7	MeOH	refux	4 h	80%
8	MeOH	MW[b], 65 °C	8 min	95%
9	MeOH	MW[b], 65 °C	25 min	85%[d]
10	MeOH	MW[b], 50 °C	10 min	50%

[a] reaction was performed using **5a** (1 mmol), **6a** (1.1 mmol), **4** (2.5 mol%), [b] Microwave reactions were carried out in Microwave Model No. CATA R (Catalyst systems, Pune) using power 280 watt, [c] Yield of the isolated product, [d] reaction was repeated with 2 mol%.

To enhance the reaction efficiency, the same reaction was performed under microwave irradiation. The reaction that was performed in MeOH solution at 65 °C under microwave heating took 8 minutes for completion with 95% yield of product **7a** (Table 1, entry 8). It is interesting to observe that the yield of the product 7a did not increase with decreasing the catalyst loading up to 2 mol% under microwave irradiation which took 25 minutes for completion (Table 1, entry 9). However, the reaction did not go to completion on lowering the reaction temperature at 50 °C (Table 1, entry 10). The results clearly established the role of MeOH as reducing agent for the reduction of ionic liquid supported Cu(II) catalyst to Cu(I) precatalyst as the reaction did not yield any Glaser reaction product, 1,4-diphenylbuta-1,3-diyne. To fully consolidate our result that the MeOH acts as a reducing agents for the in situ conversion of Cu(II) to Cu(I) during the course of the 1,3-dipolar cycloaddition reaction for, we have performed the X-ray photoelectron spectroscopic (XPS) analysis of ionic liquid supported Cu(II) catalyst before and isolated intermediate. In figure 2a, the ionic liquid supported Cu(II) catalyst **4** displayed peaks at 934.2 eV, and 953.7 eV attributed for the Cu^{2+} $2p_{1/2}$ and Cu^{2+} $2p_{3/2}$ state respectively.[24] We isolated the intermediate catalyst during the course of the reaction and carried out the XPS analysis which is shown in the figure 2b. In figure 2b, we observed small peaks at 931.4 and 951.4 eV which correspond to the Cu^{+} $2p_{1/2}$ and Cu^{+} $2p_{3/2}$ state respectively. This observation confirms the generation of Cu(I) state from methanol mediated *in-situ* reduction of Cu(II) state which is the active catalyst for click reaction.

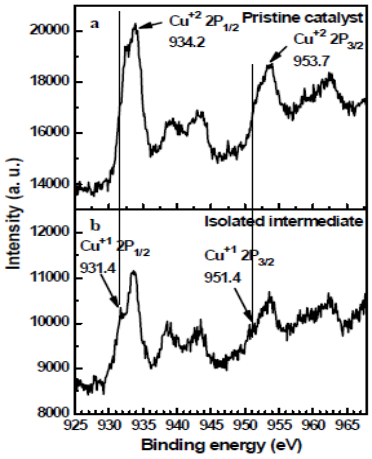
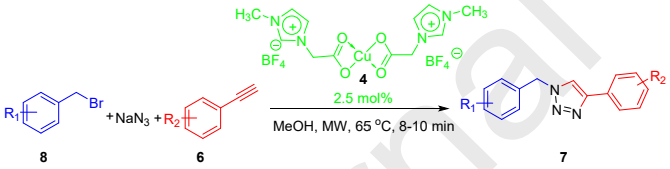


Figure 2. High resolution XPS spectra of Cu 2p in ionic liquid supported Cu(II) catalyst before and after the reaction.

After the successful synthesis of 1,4-disubstituited 1,2,3-triazole derivatives, we aimed to develop a one-pot multi-component synthetic strategy from commercially available benzyl bromide, NaN_3, and alkynes. Because of the highly explosive nature of benzyl azide, it is always important to develop the one-pot methodology without isolating and handling of this potentially harmful chemical. We have decided to carry out a one-pot two-step process for the regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles **7** from substituted benzyl bromide **8**, NaN_3 and alkynes **6** in scheme 2. Initially, substituted benzyl bromide first reacts with NaN_3 in methanol solution at room temperature for 10-15 minutes to convert into an azide, The *in-situ* generated azide further reacts with a terminal alkyne in the presence of 2.5 mol% of ionic liquid supported Cu(II) catalyst **4** at optimized reaction condition for 8-10 minutes to generate the corresponding 1,4-disubstituted 1,2,3-triazole regioselectively.[26]

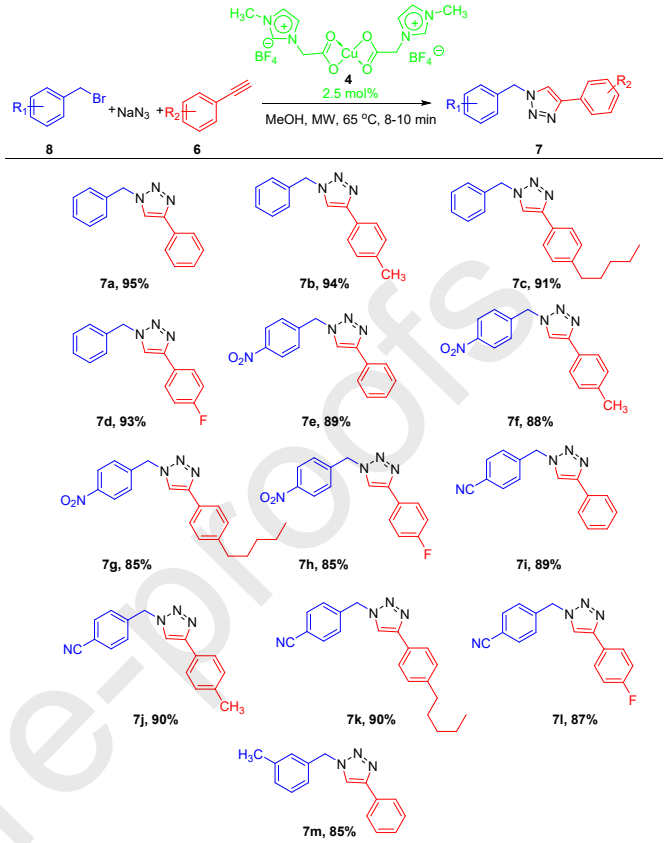


Scheme 2. One-pot multicomponent strategy for the regioselective synthesis of 1,4-disubstututed 1,2,3-triazoles**.**

After completion of the reaction, the reaction mixtures were precipitated with cold ether and filtered through fritted funnel to obtain the ionic liquid supported Cu(II) catalyst **4** followed by washing and solvent evaporation. Finally the crude products were purified by column chromatography followed by spectroscopic characterization using ^{1}HNMR, ^{13}C NMR, and mass spectroscopy (MS).

With a set of optimized multicomponent reaction conditions in hand, we examined the substrate scope with respect to various benzyl bromide and alkynes derivatives, and the results are reported in the table 2. Initially, we examined the effect of benzyl bromides or substituted benzyl bromides containing electron withdrawing groups reacted slowly to obtain corresponding triazoles in good yields. Subsequently, the substituted benzyl bromide with electron donating group reacted nicely to obtain the corresponding triazole in good yield. Further, it has been observed that aromatic alkynes containing electron-withdrawing group such as F substituents have no effect on the outcome of the reaction.

Table 2. Substrate scope for the synthesis of 1,4-disubstitited 1,2,3-triazoles.[a,b]



[a] reaction was performed using **8** (1 mmol), NaN_3 (1.1 mmol), **6** (1.1 mmol), **4** (2.5 mol%),
[b] Yield of the isolated product,

A plausible mechanistic pathway for this 1,3-dipolar cycloaddition reaction is outlined in figure 3. The first step involves the formation of *in-situ* azides from the reaction of organic halides and NaN_3 in methanol. The second step was the addition of Cu(II) catalyst and reduced to Cu(I) species by methanol followed by the addition of alkynes formed the five-membered copper metallacycle **A**. Subsequent protonolysis of intermediate **A** generates the 1,4-disubstituted 1,2,3-triazole product and arial oxidation to Cu(II) species again formed completes the catalytic cycle.

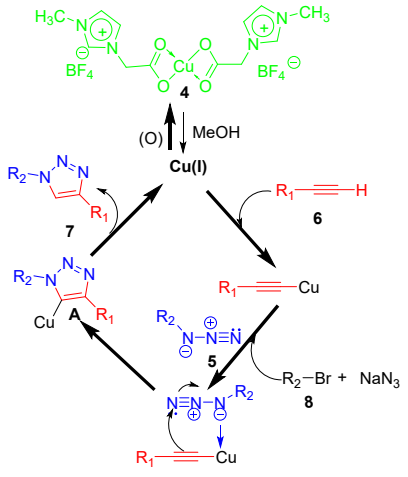
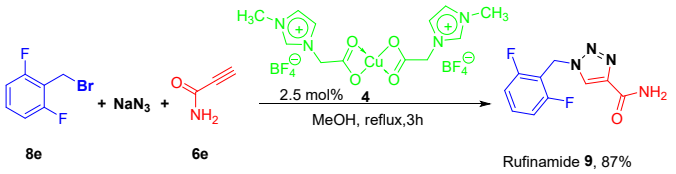


Figure 3. Plausible mechanism for the ionic liquid supported Cu(II) catalyzed 1,3-dipolar cycloaddition reaction.

was also examined. After finishing one run of reaction, another cycle of the reaction was carried out using the same catalyst **4**. It has been observed that the ionic liquid supported Cu(II) catalyst **4** is effective and recyclable catalyst for the 1,3-dipolar cycloaddition reaction leading to the regioselective synthesis of 1,4-disubstituted 1,2,3-triazole **7a** with excellent yields of 75-80% after third cycle of reaction.

After successfully conducted the regioselective syntheses of 1,4-disubstituted 1,2,3-triazoles, we plan to extend our methodology for the synthesis of rufinamide **9** as antiepileptic drug, through this multi-component synthetic strategy. The previous synthetic methodologies involved for the synthesis of this drug molecule via multistep procedures, and its synthesis requires the use of a high temperature (135 ºC) and long reaction times typically more than 24 hour.[25] The synthetic conditions are tedious and involved the use of explosive azides.



Scheme 3. One-pot multicomponent synthesis of rufinamide using ionic liquid supported Cu(II) catalyst.

We decided that rufinamide **9** could be synthesized through a multi-component reaction by employing 2,6-difluorobenzyl bromide **8e**, NaN_3, and propiolamide **6e** as shown in scheme 3 in the presence of ionic liquid supported Cu(II) **4** as the catalysts. Interestingly, the product yield of designed rufinamide **9** was obtained in 87% yield in 3h at refluxing methanol solution. The synthesis demonstrated the huge advantage of using ionic liquid supported Cu(II) catalyst for the synthesis of this drug molecule.

3. Conclusions

In summary, we have developed a versatile synthetic strategy for 1,4-disubstuituted 1,2,3-triazole derivatives through an ionic liquid supported Cu(II) catalyst precatalyst in methanol under microwave irradiation. Further, the catalyst is thermally stable, green, easy to prepare, and devoid of any drawback normally associated with homogeneous catalysts. The key features of the present protocol was the *in-situ* reduction of ionic liquid supported Cu(II) catalyst to Cu(I) followed by the formation of 1,2,3-triazole moieties in one-pot multicomponent pathway. The synthetic manipulation demonstrates the sufficient substrate scope, high yields and environmentally benign conditions. Further, the use of microwave irradiation in the present synthetic sequence demonstrated the dramatic reduction of reaction times in minutes with excellent yields and high selectivity. This synthetic methodology can open up avenues for further development of various diverse heterocycles catalyzed by ionic liquid supported Cu(II) catalyst. Finally, the current synthetic protocol useful for the one-pot synthesis of an antiepileptic drug rufinamide in good yield.

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26. **General procedure for the synthesis of 1-benzyl-4-phenyl-1*H*-1,2,3-triazole (7a):** In a round bottomed flask, a mixture of benzyl bromide **8a** (0.050 g, 0.29 mmol, 1.0 equiv) and NaN_3 (0.021 g, 0.32 mmol, 1.1 equiv) in 5 mL of mthanol. After the mixture was stirred for 10 min at room temperature, 2.5 mol% of ionic liquid supported Cu(II) catalyst **4** was added followed by phenyl acetylene **6a** (0.033 g, 0.32 mmol, 1.1 equiv) was added into the solution. The reaction mixture was irradiated under microwave heating at 280 watt for 8 min at 65 ºC. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was precipitated with cold ether, filtered through a fritted funnel to remove the catalyst. The combined filtrate was removed under reduced pressure followed by the aqueous workup. The combined organic layer was dried over anhydrous $MgSO_4$. The combined filtrate was subjected to evaporation followed by column chromatography to obtain the pure compound 1-benzyl-4-phenyl-1*H*-1,2,3-triazole **7a** as the product.

Supplementary Material

Experimental procedures, compound characterization data and copies of NMR spectra for all products are included in Supplementary data. Supplementary data associated with this article can be found in the online version.

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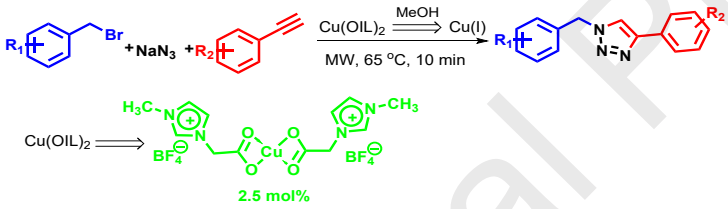

Highlights

- One-pot multicomponent reaction
- In-situ reduction of $Cu^{2+}$to Cu^{+} and confirmed by XPS analysis
- Recyclability and microwave assisted synthesis
- Application for the synthesis of Antiepileptic drug rufinamide