Cu salts-free mechanochemical approach towards multi-functionalized 1,2,3-triazoles and anti-seizure drug Rufinamide analogs

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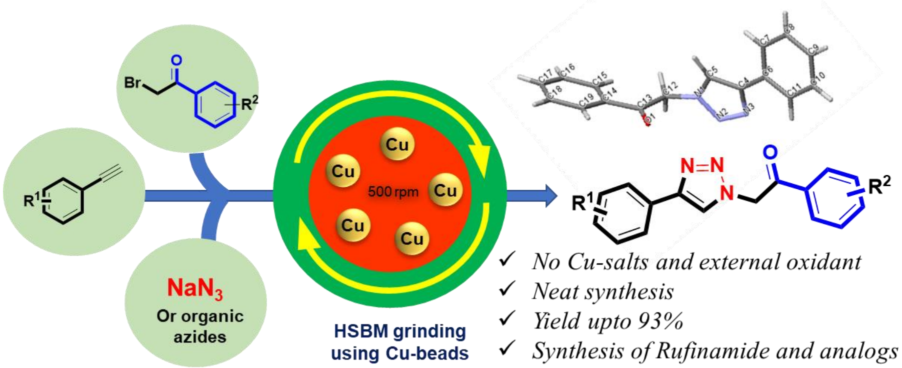
Dedicated in memory of my father Late Mr. Ratan Kumar Bhattacherjee.

Graphical Abstract



- ✓ *No Cu-salts and external oxidant*
- ✓ *Neat synthesis*
- ✓ *Yield upto 93%*
- ✓ *Synthesis of Rufinamide and analogs*

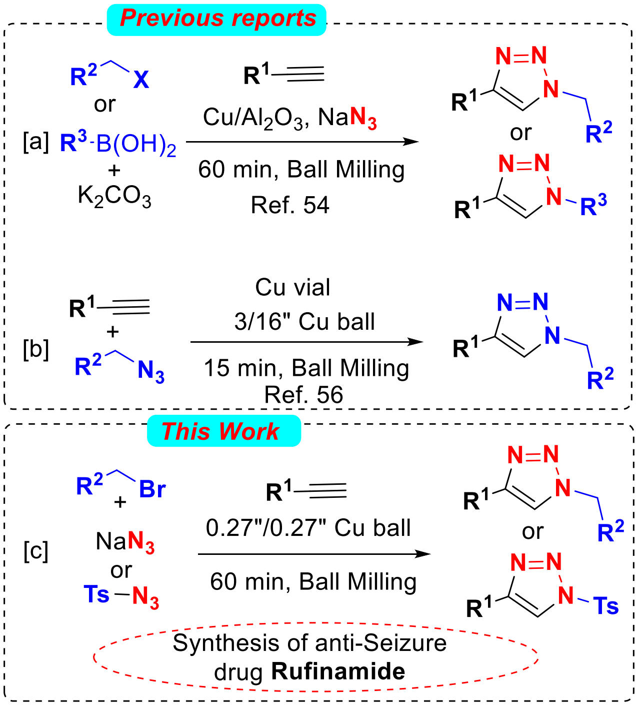
Abstract

Highly regiospecific, copper salts-free and neat conditions have been demonstrated for the 1,3-dipolar Azide-Alkyne Cycloaddition (AAC) reactions under mechanochemical conditions. A group of structurally challenging alkynes and heterocyclic derivatives was efficiently implemented to achieve highly functionalized 1,4-disubstituted-1,2,3-triazoles in good to excellent yield by using the Cu beads without generation of unwanted byproducts. Furthermore, high-speed ball milling (HSBM) strategy has also been extended to the synthesis of commercially available pharmaceutical agent, Rufinamide, an antiepileptic drug (AED) and its analogues. The same strategy was also applied for the synthesis of Cl-derivative of Rufinamide. Analysis of the single crystal XRD data of the triazole was also performed for the final structural confirmation. The Cu beads can be easily recoverable from the reaction mixture and used for the further reactions without any special treatment.

Keywords: Click chemistry; Mechanochemical synthesis; 1,2,3-Triazole; Cycloaddition reaction; Rufinamide synthesis; Solvent-free synthesis.

Introduction

The 1,2,3-Triazoles moiety represent one of the versatile class of heterocycles because of their widespread applications as pharmaceutical agents, agrochemicals and biochemicals, polymers.[1-12] The seminal work on “click chemistry” by Huisgen followed by the further independent development by Meldal et al., and Sharpless-Fokin groups has encouraged an extensive research on the 1,2,3-triazole molecule.[13-15] Over the last two decades, plethora of repots have been documented for 1,3-dipolar azide-alkyne cycloaddition (AAC) reaction and mostly involves Cu catalysis.[16-24] The assessment transition metal catalysis for the synthesis of heterocycles is common practice in modern research. Hence, several other transition metals such as Pd, Ru, Zn, Ag, Ni, Au, etc. have also been efficiently manifested for AAC reaction.[25-40] Among the 12 principles of Green Chemistry, the use of non-toxic and/or volatile organic solvents, minimal generation of organic wastes, atom-economic synthesis and use of environmentally benign chemicals have introduced an upsurging interest in contemporary organic synthesis. This field also emerging with the use of various nonconventional energy sources such as microwave, ultrasound, mechanical mixing, electrochemical methods and visible light driven organic transformations.[41] Complementing solution-based synthesis, the mechanochemical operations provide an environmentally benign alternative to negate the demand for bulk organic solvents thereby found its application in a plethora of organic transformations.[42-48] In broader sense, the application of mechanical energy such as compression, shearing or friction under solvent free conditions have been a promising technique for the utilization of mechanoresponsive materials to access active pharmaceutical ingredients (API) and thereby making a strong impact for pharma industries.[49] This technique also provides a cleaner source of energy for the organic transformations. In 2011, the planetary ball mill was used by the Schubert et al., for the solvent free AAC reaction using catalytic amount of Cu(OAc)2 and sodium ascorbate.[50] Later on, several reports for the solvent free synthesis of 1,2,3-triazoles have been encountered in which homogeneous Cu catalyst or stoichiometric amount of Cu powder were used.[51-53] To enhance the catalyst regeneration in these reactions, the immobilization of copper on the heterogenous matrix has been employed. In 2013, Ranu and co-workers efficiently demonstrated Cu/Al2O3 as catalyst for the AAC reaction under ball milling without using any solvent and additive.[54] Recently, Amini et al., showed the catalytic activity of immobilised Cu NPs on WO3 surface for the AAC reaction under solvent free conditions.[55] First time, Mack laboratory introduced the use of Cu-vial and 3/16” Cu ball for the efficient AAC reaction under 16 hours milling in solvent free conditions.[56]



Scheme 1. Mechanochemical strategies of CuAAC reaction.

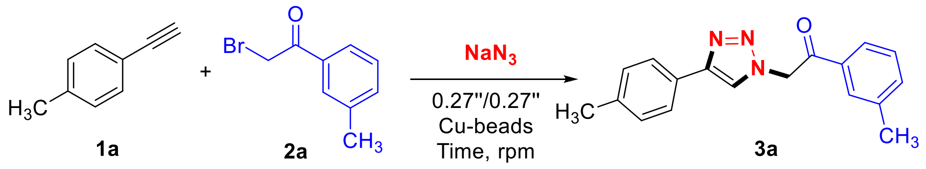
In their strategy, three component reaction such as phenylacetylene, benzyl bromide and sodium azide on grinding for 16h afforded the desired 1-benzyl-4-phenyltriazole in quantitative yield under the one-step, one vial multicomponent CuAAC reaction.

Epilepsy is a chronic neurological disorder in brain and affecting people of all ages worldwide. Rufinamide (brand name Banzel[57] or Inovelon[58], developed by Novartis and manufactured by Eisai) has been already reported as a sodium channel blocker and an antiepileptic drug (AED) having broad spectrum of efficacy. It is FDA approved orphan drug used for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS). The common strategies for the synthesis of Rufinamide involves 1,3-dipolar cycloaddition reaction using 2-chloroacrylonitrile, propiolic acid and esters or (E)-methyl 3-methoxyacrylate.[59-64] Recent synthetic developments involve flow microreactor systems via multistep synthesis in a compartmentalized continuous flow integrated with in-line separation techniques.[65-68] We envisioned that Mechanochemical conditions could be useful for the synthesis of Rufinamide and its analogs via [2+3] CuAAC reaction and, to the best of our knowledge, this approach is still uncommon in a literature. Herein we wish to report a Mechanochemical strategy of 1,3-dipolar Huisgen cycloaddition of various azides, generated in-situ, with a dipolarophile (alkynes) to construct structurally important 1,2,3-triazoles as well as Rufinamide and its analogs by using Cu-beads.

Results and Discussion

At the commencement of our investigation, we have chosen 4-ethylnyl toluene (1a) and 2-bromo-1-(*m*-tolyl)ethan-1-one (2a) as bench stable substrates to react in the presence of inorganic azide. Different Mechanochemical parameters of the reaction such as time, rpm limit, equivalency, and number of copper balls were optimized in order to obtain the desired 1,2,3-triazoles in a highest yield. The results of the optimization of the Mechanochemical reaction conditions are reported below (Table 1). Thus, we have observed that the **1a** (50mg, 0.431mmol), **2a** (183.6mg, 0.862mmol) and NaN_3 (56mg, 0.862mmol) is satisfactorily afforded **3a** in 86% of yield under neat reaction conditions for 3h of Mechanochemical grinding with 5 Cu-beads at 500 rpm (Table 1, Entry 4). Intriguingly, the overall yield of the triazoles also depends on the number of Cu-beads in the reaction (Figure 1). The Cu balls are highly useful to catalyse the reaction. When the same reaction were carried out in using teflon balls in absence of Cu balls, trace quantity of product formation was not observed (Table 1, Entry 8). These conditions were useful for the further assessment of the various alkynes and benzoylmethyl bromides. We have not observed much electronic control of different alkynes as well as benzoylmethyl bromides over the reaction yield for three component reactions and products 3b-d were obtained in 63-73% yield. In all the cases we have isolated unreacted starting alkynes in small quantities. In the case of biphenyl acetylene the observed yield of the product **3e** was 42% and the conversion of the starting material was poor. The poor yield may be attributed to the three-component reaction in presence of un-activated copper beads as well as low reactivity of sterically and electronically unfavorable alkyne species. Changing the equivalency or the grinding time did not

Table 1. Mechanochemical optimization of reaction parameters.[a]



Entry	Equiv. of azide	RPM	Time (h)	Conversion (%)	Selectivity (%)	Yield (%)[b]
1	1.2	300	1	68	35	24
2	1.2	400	2	80	70	56
3	1.2	500	3	88	89	79
4	2.0	500	3	98	88	86
5	2.0	500	4	98	88	86
6	2.0	400	3	82	78	64
7	2.4	500	3	98	88	86
8[c]	1.2	500	2	0	0	nr

[a]Reaction conditions: **1a** (0.431 mmol), **2a** (0.862 mmol), sodium azide (0.862 mmol), 5-Cu beads, 500 rpm; [b]yields refer after chromatographic purification.[c]reaction carried out in presence of teflon balls.

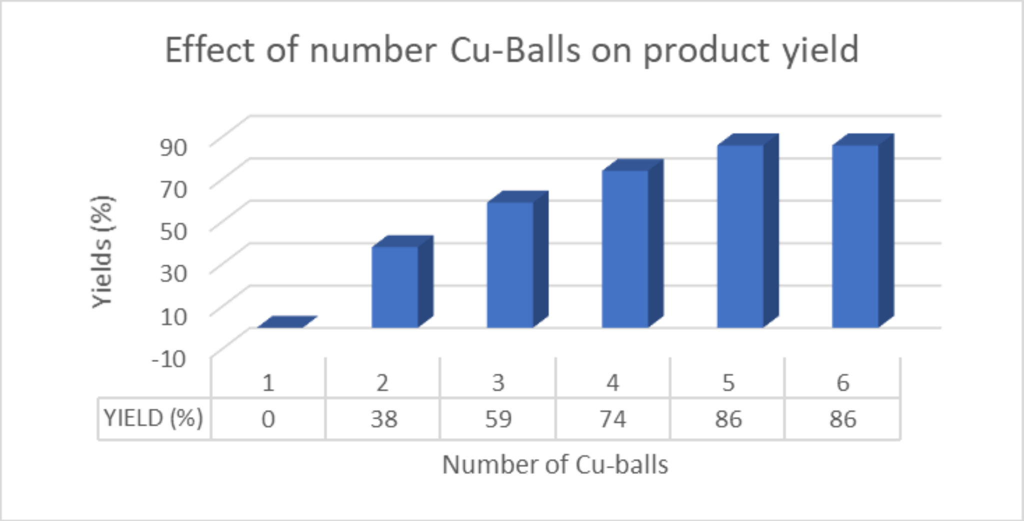
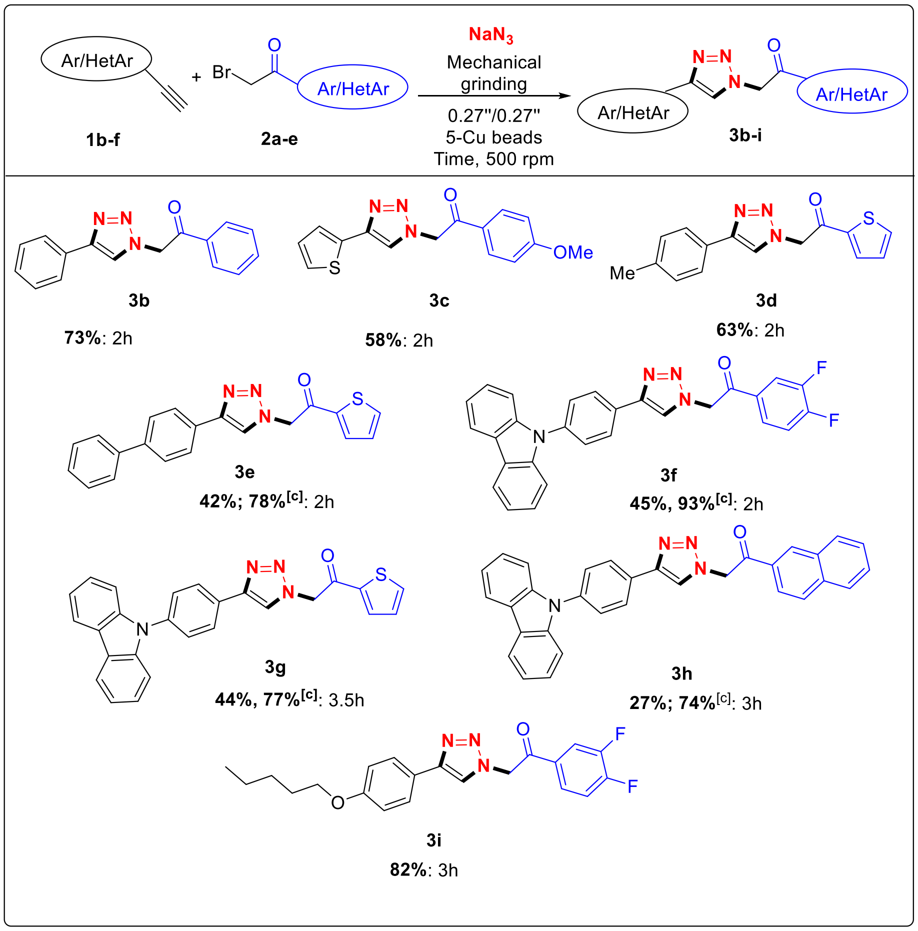


Figure 1. Effect of cylindrical Cu-beads (0.27/0.27″) on the product yield.

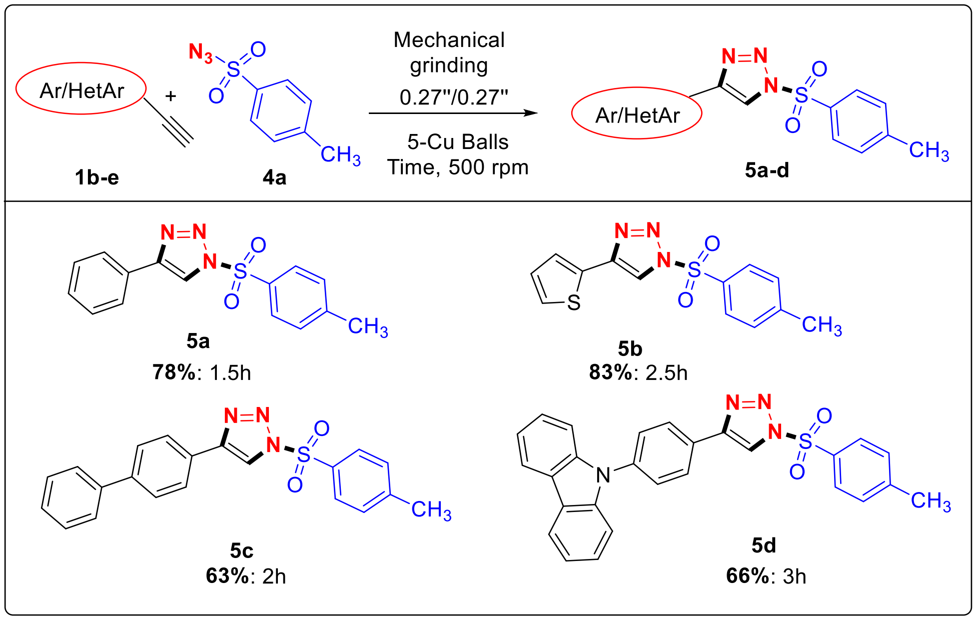
Table 2: Scope of various alkynes and benzoylmethyl bromides in mechanochemical CuAAC reaction.[a,b]



[a]**Reaction conditions**: Ar/HetAr alkynes **1b-f** (1 equiv.), benzoylmethyl bromides **2a-e** (1.2 equiv.), sodium azide (1.2 equiv.), 5-Cu beads, 500 rpm; [b]yields refer after purification; [c]stepwise route; [d]minute quantity of THF were added for dissolution of solid component.

improve the yield of the desired product significantly. To our delight, excellent yield of **3e** was found by changing the reaction fashion. The same reaction was carried out in a stepwise fashion in which first the benzoylmethyl bromide derivatives were converted into corresponding azido derivatives (See supporting information) and then employed under optimized mechanochemical conditions. Then we have introduced structurally interesting and highly sterically hindered alkynes (1f-i) for the anticipated CuAAC reaction. Under the conditions of three component coupling, we have again encountered low to moderate yield for the compounds **3f-i** (Table 2). However, the stepwise fashion of the mechanochemical reaction gave excellent yield of the products **3f-i** (Table 2). In all these reactions, benzoylmethyl bromide derivatives have no marked effect on the yield of the final 1,2,3-triazole derivatives (Table 2). It is noteworthy that the Mechanochemical synthesis of 1,2,3-triazole lead to the formation of only 1,4- regioisomers and formation of 1,2-isomers were not observed. Owing to the inherent biological activity of the sulphonamides, we have targeted triazole based sulphonamides molecules under Mechanochemical conditions (Table 2). We have encountered the low yield of the products in case of three component Mechanochemical coupling of alkynes, sodium azides and tosylchlorides. Therefore, the tosylazides (4a) were prepared using reported conditions (supporting information) and then employed in the 1,3-dipolar cycloaddition. In all the cases moderate to good yield of the triazole based

Table 3: Scope of various alkynes in CuAAC with tosyl azides under Mechanochemical conditions.[a]



1b-e **4a** **5a-d**

5a
78%: 1.5h

5b
83%: 2.5h

5c
63%: 2h

5d
66%: 3h

[a]Reaction conditions: Ar/HetAr alkynes **1b-e** (1 equiv.), tosyl azide **4a** (1.2 equiv.), 5-Cu beads, 500 rpm; [b]yields refer after purification.

sulphonamides **5a-d** were observed. Interestingly, formation of only 1,4-regioisomer was observed with excellent selectivity.

Finally, to confirm the structure of the obtained products, the single crystal XRD experiments were carried out for the 1,2,3-triazole **3b** and the obtained single crystal XRD structure is presented below (Figure 2).

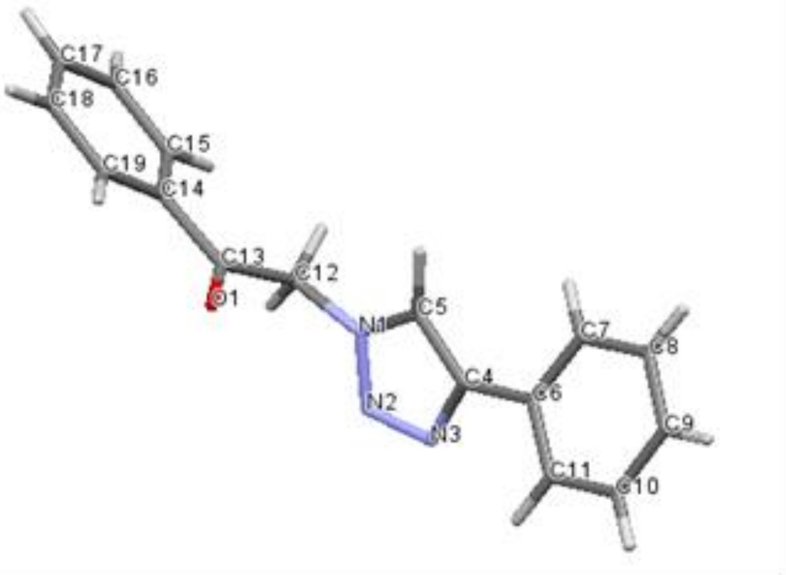
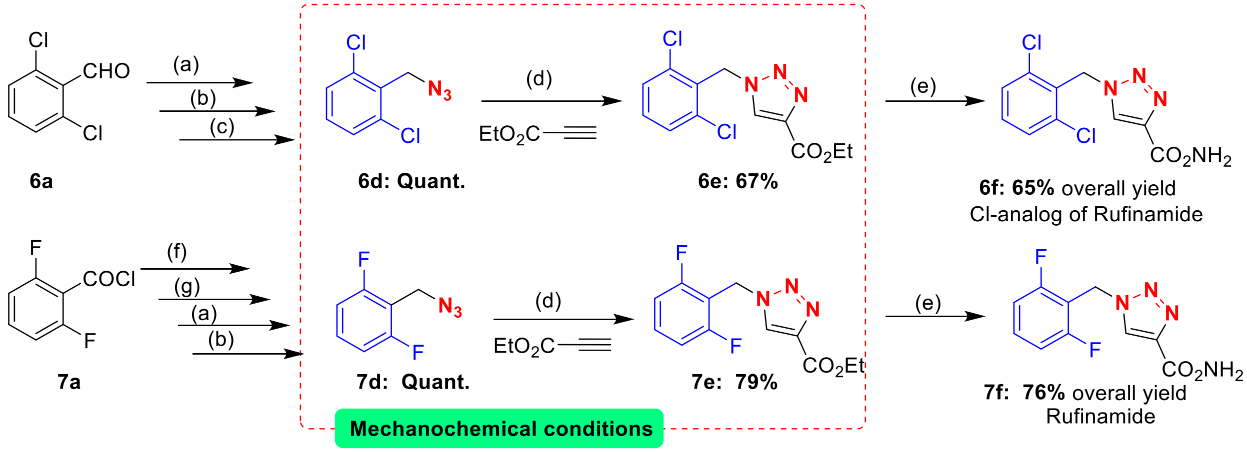


Figure 2. Single crystal XRD structure of **3b**.

To demonstrate the synthetic utility of the present reaction, we have successfully prepared the Rufinamide (compound **7f**), a commercially available antiepileptic drug (AED) and its Cl-analogue (compound **6f**) in good overall yields (Scheme 2). The Cl-analogue of Rufinamide drug was prepared by starting from easily available 2,6-dichloro benzaldehyde precursor followed by the synthesis of 2,6-dichlorobenzyl azides (Supporting information). Without any tedious purification of these organic azides, we have treated with propiolic esters under our optimised mechanochemical grinding using copper beads. The ethyl ester of the propiolic acid under our optimised mechanochemical conditions gave the formation of desired 1,4-isomer only compared to methyl ester derivative of propiolic acid derivatives. To our delight, we have observed formation yellow crude after the reaction which contains only 1,4-regioisomer (**6e**) as a major product and gave after purification in 67% yield. We have also observed that the mechanochemical conditions gave better result in case of two component reaction *i.e.*, alkyne and organic azide rather than three. The triazlic esters (**6e**) can be easily converted into the amide derivatives by the treatment with ammonia water in methanol. Similar experimental procedure was followed for the synthesis of commercially available drug Rufinamide **7f** in 79% of overall yield with greater selectivity (Scheme 2).



Reaction conditions: (a) $NaBH_4$ (2.5 equiv.) in CH_3OH for 2h at rt; (b) PBr_3(1.1 equiv.) in DCM at 0ºC for 12h; (c) NaN_3 (4 equiv.) in acetone/water for 6h at rt; (d) Alkyne (0.8 equiv.), Azide (1.0 equiv.), Mechanical grinding: 0.27″/0.27″ 5-Cu beads, 500 rpm, 2h; (e) NH_4OH in CH_3OH under reflux; (f) NEt_3 (1 equiv.) in ethanol at 60ºC for 2h; (g) $LiAlH_4$ in dry THF at 60ºC for 2h.

Scheme 2. Total synthesis of anti-seizure drug Rufinamide and analogues.

Plausible Catalytic Pathway: From the discussions we have observed the *in-situ* generation of stable and isolable organic azides (II) as are the key intermediate followed by the 1,2,3-triazole formation. In some cases, we have also performed reaction between the alkynes and organic azides to enhanced the overall yield. Based on the previous literature reports[69-72] and the above experimental findings, a plausible reaction mechanism is suggested as shown in Figure 3. The proposed catalytic cycle for the AAC of alkynes with the azides consists of an initial copper acetylide formation to afford intermediate **I**. We surmised that, in the catalytic cycle, NaN_3 can change the valence state of Cu during the reaction and that this might be responsible for the observed activity.[73-74] The Cu(I) species reacts with an alkyne to give a copper acetylide. On the other hand, benzoylmethyl bromides reacts with sodium azides to form benzoylmethyl azides **II** which are one of the key intermediate in the catalytic cycle. The 1,3-dipolar cyclization of the resulting Cu acetylide **I** and benzoylmethyl azides **II** followed by the protonation provided the formation of target 1,2,3-triazole **V** and the regeneration of Cu catalyst. It worth to mention that, Cu-beads are recyclable, and after the sonication with acetone the Cu-beads can be returned the reaction without loosing the both the grinding performance and the catalytic activity.

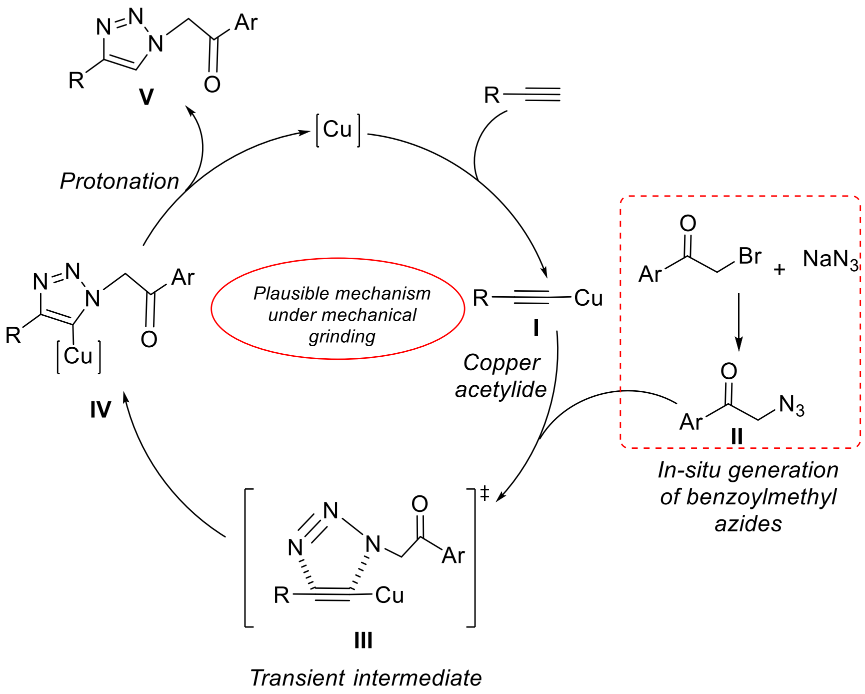


Figure 3. Plausible reaction pathway of the Huisgen cycloaddtion.

Conclusion

In summary, we have developed a regiospecific, environmentally benign mechanochemical grinding for 1,3-dipolar Huisgen cycloaddition reaction between terminal alkynes and azides using Cu-beads. Highly functionalized 1,2,3-triazoles were prepared selectively in good to excellent yield by easy workup technique and without generation of unwanted waste. This energy and cost-effective process have also been extended for the synthesis of Rufinamide, a commercially available antiepileptic drug (AED) and its Cl-analog. The crystallographic data of the triazole molecule also established for structural confirmation. Furthermore, the *insilico* studies of the prepared molecules are still under investigation and the results will be published in the due course. Finally, this research would encourage the synthetic community for the development of active pharmaceutical ingredients using greener energy sources and impact the pharma industries.

Author Contributions

DB conceptualized, investigated, and involved in formal data analysis as well as scientific manuscript writing. ISK and DSK involved in the methodology development concept, MR and SS were involved in the formal data analysis. GVZ, PD, RP, VLR and ONC conceived and supervised the project. All authors edited and agreed to the final version of the manuscript.

Experimental Section

General experimental procedure for the mechanochemical cycloaddition reaction: PM100 stainless steel grinding bowl having internal volume 25 mL containing 0.27/0.27inch cylindrical copper beads (5 beads) was charged with Alkynes (1 equivalent) and equimolar quantities of benzoylmethylbromide (2 equivalent otherwise mentioned) and sodium azide (2 equivalent otherwise mentioned).The grinding bowl was then equipped with stainless steel bowl cap and placed in the mechanical ball milling instrument. The reaction mixture within the grinding bowl allowed to rotate for 3 hours (otherwise mentioned) at the speed of 500 rpm. The progress of the reaction was monitored by the TLC and the reaction mixture was extracted with dichloromethane. The crude was concentrated under reduced pressure and the product was isolated using silica gel(230-400) column chromatography under hexane/ethylacetate gradient.

Acknowledgements

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