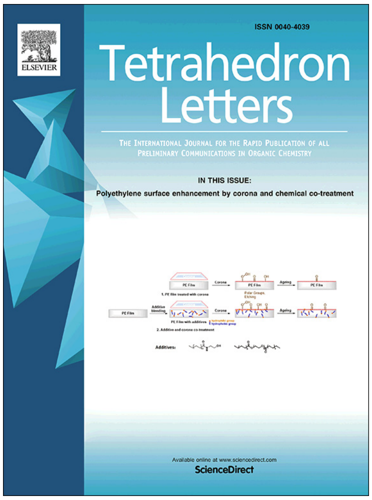

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Graphical Abstract

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An efficient synthesis of fluorescent 1,4-disubstituted triazoles using L-phenylalanine as an accelerator ligand at ambient temperature in aqueous media

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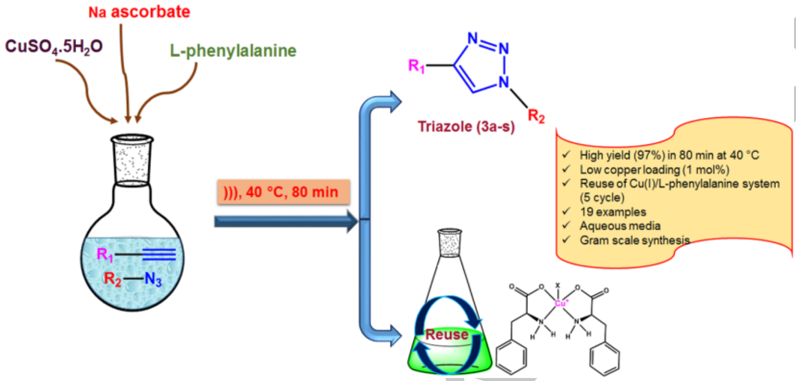
Yachana Jain[a], Mitlesh Kumari[a], Ragini Gupta[*, a, b]



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Sonochemical synthesis of fluorescent 1,4-disubstituted triazoles using L-phenylalanine as an accelerator ligand in aqueous media

Yachana Jain[a], Mitlesh Kumari[a], Ragini Gupta[*, a, b]

[a] *Department of Chemistry, Malaviya National Institute of Technology Jaipur 302017, India*
[b] *Materials Research Centre, Malaviya National Institute of Technology Jaipur 302017, India*

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ABSTRACT

A green sonochemical protocol using L-phenylalanine as a water soluble promotor ligand has been developed for the regioselective synthesis of fluorogenic 1,4-disubstituted triazoles (3a-o) *via* well-known click reaction at 40 °C. L-phenylalanine is a biocompatible, economical, commercially available and non-toxic ligand which not only serves to stabilize Cu(I) oxidation state but also prevents its disproportion to enhances and modulate the rate of reaction. The designed catalytic system exhibits broad substrate compatibility and can be recycled up to 5 cycles without appreciable loss in the yield of desired product. Gram scale synthesis was successfully accomplished with 92% yield.

Indroduction

1,3-dipolar cycloaddition reaction between azides and terminal alkynes for the synthesis of substituted five membered triazoles ring containing three nitrogen atoms has attained great impetus since its inception by Huisgen[1] and further made regioselective by nobel laureate Sharpless-Fokin[2] and Meldal[3] group using Cu(I) catalyst. It is one of the most proficient coupling strategies for making C-N bonds adopted for its bioorthogonality, simplicity, efficiency, high reliability, wide scope, and functional group tolerance making it a reaction of choice for biologists and chemists[4, 5]. Nevertheless, an increasing alertness for the development of more sustainable approach for synthetic chemistry in industries and scientific community, numerous environmental friendly approaches have been recognized. From the click chemistry point of view polar solvents such as DMF, ACN, DMSO, DCM, THF, and ^{t}BuOH, $CHCl_3$, MeOH are frequently used to carry out reaction[6, 7]. Only water as a media is in high demand since it is cheap, easily available, non-inflammable, non-toxic and more abundant[8]. Therefore, development of new strategy for organic reaction to proceed reaction in water is challenging task for scientific community.

Recently, many approaches have been applied to modify Copper catalyzed Azide-Alkyne Cycloaddition (CuAAC) reaction like using water as reaction media, use of ultrasound waves[9, 10], microwave irradiation. Numerous other techniques have also been developed including solid supported catalyst[11], photo catalysis, ligands and other additives for synthesis of regioselective triazoles. To improve the activity of copper catalysts and to reduce the amount of copper, various ligands have been developed since they play an important role in promotion of the reaction rate by coordinate to copper and stabilizing it as Cu(I) ions and shielding from air oxidation and preventing its disproportionation. Cu-binding ligands containing oxygen, sulphur, nitrogen, phosphorus atoms such as TBTA, THPTA[12, 13], AMTC[14], betain[15], sulphide ligands, histidine, polysaccharide-supported nanoparticles[16], N-heterocyclic carbenes[17], poly nitrogen ligands[18, 19], Urea[20], and tri(aminoalkyl)amine[21].

However, these methods have great advances in reducing of copper amount but still they have some shortcomings. For instance, tedious synthetic procedure, use of an excess amount of reductants and use of organic solvents.

A few reports are available for water soluble ligands like THPTA[12, 13], AMTC[14], Urea[20]. There is still need to develop a sustainable approach to meet growing demand of green chemistry.

In this context, many amino acids (AA) also have been used as a ligand because they have diverse functional groups such as amino, carboxyl, phenolic, imidazole, and phenyl which can form chelates with different metal ions. Amino acids are water soluble, readily available, low cost, biocompatible, stable and non-toxic in nature. Pezacki *et. al* reported that

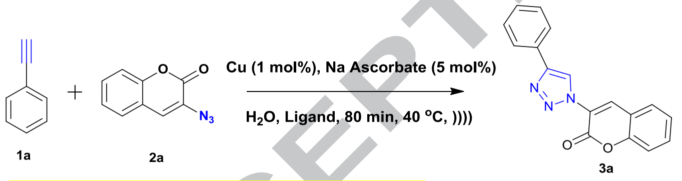
Cu(I)-L-histidine ligand serves as an efficient ligand for catalyzing the CuAAC reaction[22]. It has been reported that two molecules of amino acids can complex with one molecule of Cu.[23]

In continuation to our research in the field of novel environmental friendly approaches in synthetic chemistry[24-27] we have successfully demonstrated a new pathway for preparation of diverse 1,4-disubstituted triazole *via* 1,3-dipolar cycloaddition reaction in water by using L-phenylalanine as a ligand of Cu(I) without using any organic solvents, at ambient temperature (no requirement of high temperature) in lesser time. L-Phenylalanine, having nonpolar phenyl group, found buried within the hydrophobic core of a protein.

Results and Discussion

The aim of the present study is to explore mild biocompatible route for synthesis of fluorescent coumarin based triazoles in aqueous media which may be suitable for bio-imaging applications in living cells therefore, a model design was envisaged to determine the optimum reaction parameters for CuAAC reaction taking phenylacetylene **(1a)** and 3-azidocoumain **(2a)** as model substrates. Initially, stirring of 1 mmol of 3-azidocoumarin (1a) 1.1 mmol of phenylacetylene, $CuSO_4.5H_2O$ (1 mol%), Na Ascorbate (5 mol%) in water (5 mL) using L- phenylalanine (2 mol%) as a promotor ligand **(Table 1, entry 1),** yielded only 60% desired product in 80 min at 40 °C. TLC monitoring revealed complete conversion into the corresponding product after 8 hr. Considering the synthetic utility of ultrasound[28-30] the same reaction was repeated under ultrasonication with dramatic acceleration in rate of reaction furnishing 97 % yield of desired product in 80 min **(Table 1, entry 3)** (**Scheme 1)**. Screening of different copper salts established that $CuSO_4.5H_2O$ is superior in reactivity over others for this reaction **(Table 1, entries 2-6)**. It can be seen that no reaction occurred in the absence of Cu(I) regardless of the presence of L-phenylalanine **(Table 1, entry 11)**. To study the role of promotor ligand several aromatic amino acid were studied for the model reaction. Interestingly, L-phenylalanine gave the best result with high yield while other gave slightly lower yield of desired triazole **(Table 1, entries 7-9)**. It is worth to note that in the absence of L-Phenylalanine the product yield was 30% after 80 min highlighting the role of the ligand for enhancing the rate of reaction **(Table 1, entry 11)**. All the reaction proceeded in open air with no formation of noticeable side products. With these optimum reaction conditions in hand, different solvents were also investigated for CuAAC reaction using Cu(I)/L-phenylalanine catalytic system. It is apparent from the **Figure S1a,** water proved to be the best solvent for this transformation with quantitative yield in only 80 min at 40 °C. Subsequent efforts were focused on optimizing the minimum effective concentration of $CuSO_4.5H_2O$ for catalyzing the CuAAC reaction. Since copper toxicity is critical issue while expanding this strategy to living organism. Different concentrations of $CuSO_4.5H_2O$ were tried (2, 1, 0.05 mol%) for model reaction in water at 40 °C. When the reaction was performed with 2 and 1 mol% of Cu(I), conversion after 80 min was 100% and desired product was obtained in 97% isolated yield while at 0.05 mol% the yield decreased to only 80% (**Figure S1b**). Conclusively, the best conditions for the present click reaction are at 1 mol% of $CuSO_4.5H_2O$, 5 mol% of Na Ascorbate, 2 mol% of L-phenylalanine at 40 °C for 80 min under ultrasonication in aqueous media.

Table 1. Effect of different copper salt and ligands for synthesis of 1,4-disubstituted triazoles.[a]



Entry	Cu salt (1 mol %)	Na ascorbate	Ligand (2 mol%)	Yield [b] (%)
1	$CuSO_4.5H_2O$	5 mol%	L-Phenylalanine	60*
2	$CuSO_4.5H_2O$	5 mol%	L-Phenylalanine	97
3	CuI	-	L-Phenylalanine	82
4	$CuCl_2.2H_2O$	5 mol%	L-Phenylalanine	80
5	$Cu(OAc)_2.H_2O$	5 mol%	L-Phenylalanine	85
6	$Cu(NO_3)_2$	5 mol%	L-Phenylalanine	88
7	$CuSO_4.5H_2O$	5 mol%	L-Tyrosine	82
8	$CuSO_4.5H_2O$	5 mol%	L-Tryptophan	70
9	$CuSO_4.5H_2O$	5 mol%	L-Histidine	89
10	$CuSO_4.5H_2O$	5 mol%	-	30
11	-	-	L-Phenylalanine	-

[a]1 mmol of azide, 1.1 mmol of alkyne, 1.0 mol % of [Cu] and 5.0 mol % sodium ascorbate in presence of 2 mol % of ligand in H_2O (5 mL) at 40 °C. [b]Isolated yields by column chromatography.*Reaction proceeded using stirring.

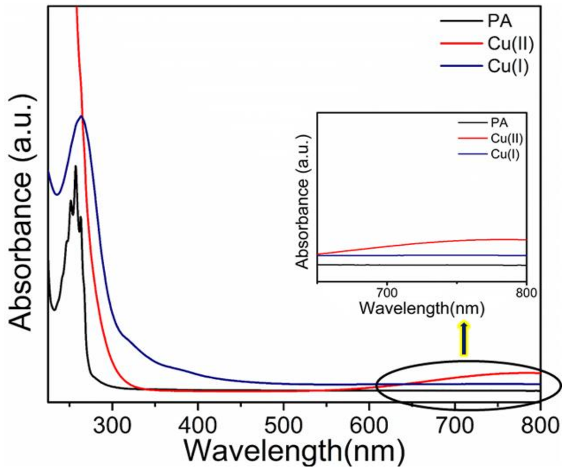


Figure 2 Role of L-phenylalanine for click reaction monitored by UV-vis. Spectroscopy.

Role of L-phenylalanine of as ligand was also confirmed by using UV-visible spectra of aqueous solution of $CuSO_4$. $5H_2O$ which shows absorption in the range of 700-800 nm **(Figure 2, inset)**, ascribed to Cu^{+2} *d-d* transition[31]. After coordination of Cu^{+2} to the ligand this absorption vanishes and further reduction (Cu^{+2} to Cu^{+1}) by Na Ascorbate exhibits a band in the range of 300-400 nm (absorption at 331 nm, **Figure 2**) which is attributed to a metal-to-ligand charge transfer transition[32].

After developing the optimized reaction conditions, the scope of this method further explored for the synthesis of regioselective 1,4-disubstituted triazole *via* 1,3-dipolar cycloadditions reaction. In this context, different derivatives of 3-azidocoumarin **(2a-e)** (electron donating and withdrawing group) and terminal alkyne **(1a-c)** were taken to prepare the corresponding 1,4-disubstituted triazole under the optimized reaction conditions **(Table 2)**. To further widen the scope of the study common substrates were also tested (**Table S2**). Analysis of the results showed that most of the substrates produced the expected triazole products with excellent conversion. Attractive attributes of the present methodology are that the click reaction is performed using water as a versatile solvent at ambient temperature, devoid of unwanted products, and recycling for five consecutive runs without appreciable loss in yield % of the desired product.

Absorbance and Fluorescence Analyses of 1,4-disubstituted Triazoles (3a-o)

Figure S4 a shows the absorption spectra of coumarin triazoles **(3a-o)** (1×10^{-5} M in DMSO solution). Absorption at around 300 nm is attributed to the π-π^* transition, which arises from the extension of conjugation by triazole ring formation[33]. A bathochromic shift in absorption is observed in the case of 6-bromo, 7-hydroxy, 5, 6-benzo and 8-methoxy substituted triazoles, which consistent with previous reports[8]. The bands around 410 nm in 7-hydroxy and 8-methoxy derivatives, is assigned to the n-π^* transition.

3-azidocoumarin derivatives **(2a-e)** are nonfluorescent because of the presence of three electron-rich azido group at the

3rd position but after clicking with different terminal alkynes **(1a-c)**, fluorescence turn on is observed due to the formation of five-membered triazole ring which extends the conjugation. It is observed that the fluorescence intensity and position vary by the presence of certain functional groups in the coumarin scaffold. Triazoles containing the -OH functional group (**3b, 3g, 3l**) at the 7th position on the coumarin moiety produces a strong emission band with maximum intensity due to the expansion of conjugation by increasing its electron density. In contrast, triazoles containing a 6-Br group (**3c, 3h, 3m**) produce a weak emission band due to first the electron withdrawing nature of bromine and second its heavy atom effect[34].

Mechanism

The plausible mechanism of the Cu(I)-catalyzed azide-alkyne cycloaddition reaction[2, 35, 36] for the formation of 3a is proposed as depicted in **Figure S2**. The Cu(II) salt is first reduced to Cu(I) by the reducing agent and then forming a Cu(I) complex with ligand. The Cu(I) catalyst first interact with terminal alkyne to form a complex A and then reacts with a second Cu(I) to generate a copper-acetylide complex B. The complex thus formed react with an azide to produce complex B *via* intermolecular cyclization leads to metallacycle D, which gets transformed into copper triazolide E after reductive elimination. Complex D undergoes protonolysis, providing the desired 1,4-disubstituted triazole and regenerating the Cu(I).

Catalytic performance where toxic copper metal involved is another side of concern from environmental concern which can be sorted out by recycling of catalyst. Since $CuSO_4.5H_2O$, L-phenylalanine, and Na ascorbate are all soluble in H_2O so it was thought useful to recycle the aqueous filtrate as such without further addition of these reagents in consecutive cycles. This theory led to positive results up to five runs. Slight decrease in %yield of desired products (**Figure S3**) may be due to loss of Cu(I) in water during workup process.

Conclusion

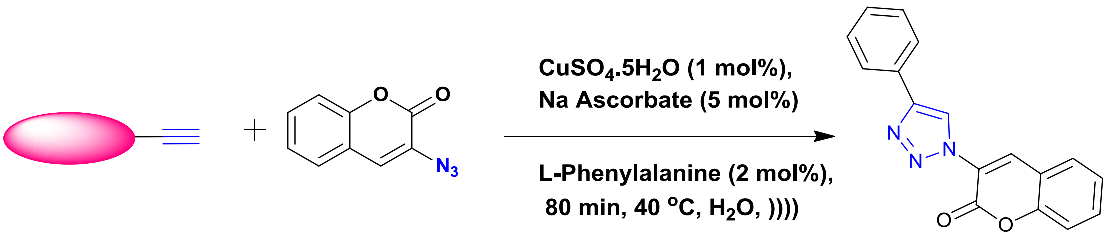
In conclusion, we have demonstrated a simple efficient and versatile protocol for regioselective synthesis of a variety of 1, 4-disubstituted triazoles from diversely substituted azide and various terminal alkyne under organic solution free conditions using L-phenylalanine as an additive. Ligands plays a key role and enforced hydrophobicity of water for the reaction. This environmental friendly protocol opens-up new door for achieving target compounds under mild conditions (less time, ambient temperature (40 °C)) to tackle future synthetic experiments and have a broad spectrum impact on biological and material sciences as L-phenylalanine is cheap, easily available, and biocompatible reagent.

Experimental

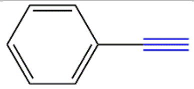
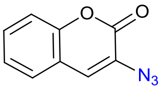
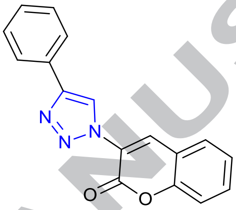
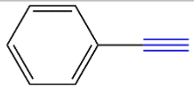
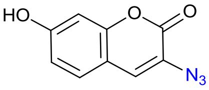
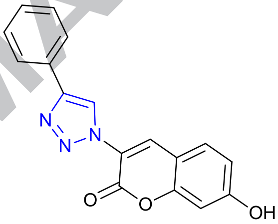
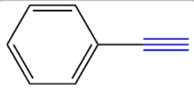
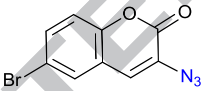
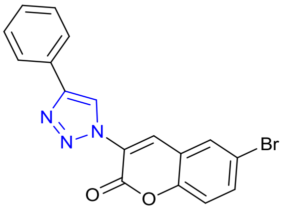
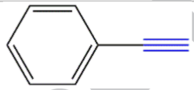
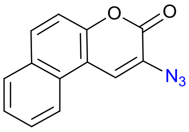
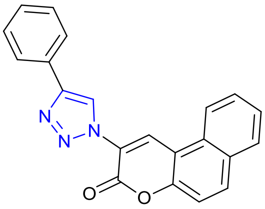
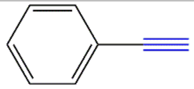
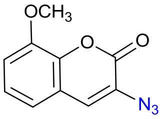
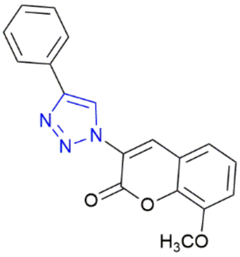
Typical procedure for the synthesis of 1,4-disubstituted 1,2,3-Triazoles (3a-o)

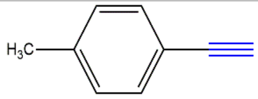
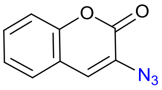
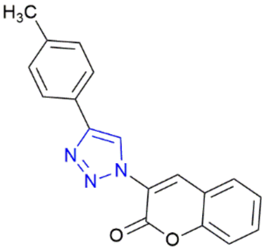
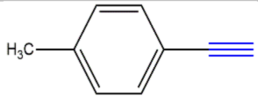
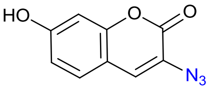
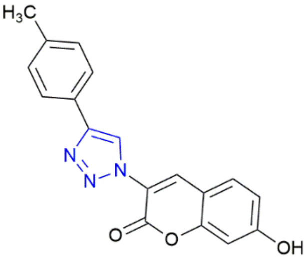
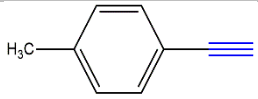
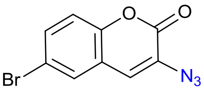
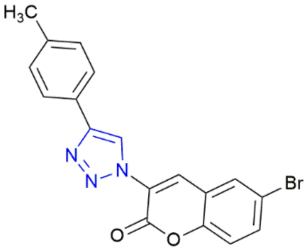
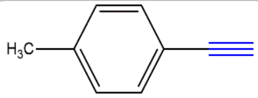
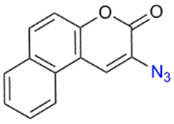
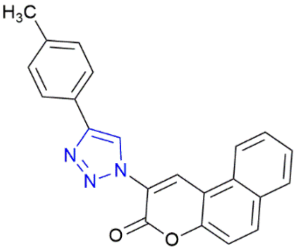
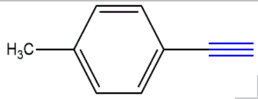
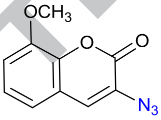
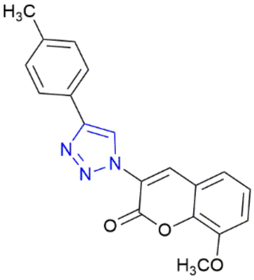
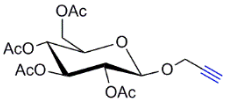
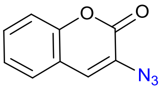
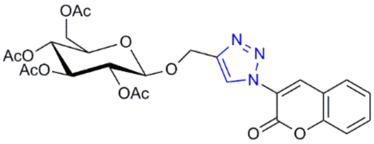
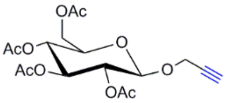
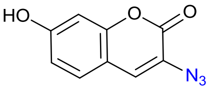
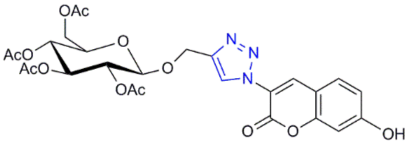
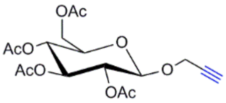
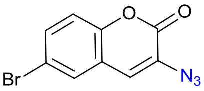
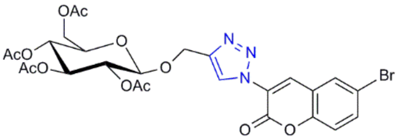
3-azidocoumarin (1 mmol, 0.1871 g) and phenylacetylene (1.1 mmol) were taken in a round bottom flask. Then $CuSO_4 \cdot 5H_2O$ (2.49 mg, 1 mol%), sodium ascorbate (9.9 mg, 5 mol%), L-phenylalanine (2 mol%, 3.3 mg) in H_2O (5.0 mL) were added into it. The resultant mixture was ultrasonicated for the time mentioned in Table 2 at 40 °C. Progress of reaction was monitored by TLC. After completion of the reaction, resultant mixture was extracted with ethyl acetate (3x10 mL) and dried over Na_2SO_4 and concentrated under reduced pressure. Removal of the solvent yielded a residue, which was purified by a flash column chromatography over silica gel (80-200 mesh) and eluted with n-Hexane:EtOAc (3:1) to furnish desired products.

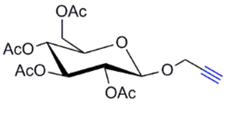
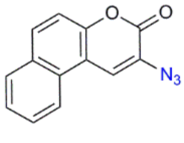
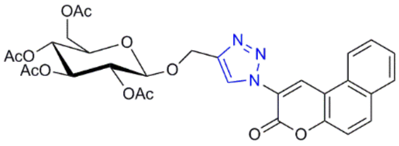
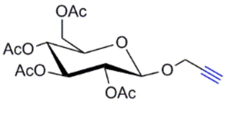
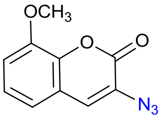
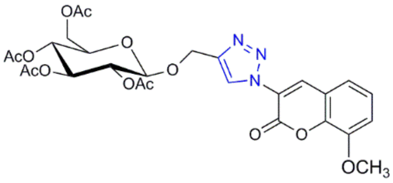
Table 2 Azide-alkyne cycloaddition reaction of various acetylene **(1a-c)** with different azide **(2a-e)** in aqueous media[a]



1a-c 2a-e 3a-o

Entry	Azides	Alkynes	Triazoles	Time (min.)	Yield (%)[b]	Product code
1	 **1a**	 **2a**		80	97	**3a**
2	 **1a**	 **2b**		85	95	**3b**
3	 **1a**	 **2c**		80	94	**3c**
4	 **1a**	 **2d**		85	92	**3d**
5	 **1a**	 **2e**		82	96	**3e**

6	 **1b**	 **2a**		85	96	**3f**
7	 **1b**	 **2b**		82	94	**3g**
8	 **1b**	 **2c**		85	92	**3h**
9	 **1b**	 **2d**		85	92	**3i**
10	 **1b**	 **2e**		80	95	**3j**
11	 **1c**	 **2a**		80	95	**3k**
12	 **1c**	 **2b**		85	92	**3l**
13	 **1c**	 **2c**		85	95	**3m**

14	 **1c**	 **2d**		90	91	**3n**
15	 **1c**	 **2e**		85	92	**3o**

[a] All reactions were carried out using 3-azidocoumarin (1 mmol), terminal alkynes (1.1 mmol), 1.0 mol % of Cu and 5.0 mol % sodium ascorbate in presence of 2 mol % of ligand in H_2O (5 mL) at 40 °C under ultrasonication. [b] Isolated yields by column chromatography

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Highlights

- Ultrasound assisted synthesis of 1, 4-disubstituted-1,2,3-triazoles at 40 °C in aqueous media.
- This protocol exploits biocompatible, easily available L-phenylalanine as a promotor ligand.
- Recyclability of L-Phenylalanine/Cu(I) system up to 5 cycles.
- High product yield (up to 97%) in lesser reaction time (80 min).
- Gram scale synthesis