

Synthetic Strategies for 1,2,3-Triazole Based Bioactive Compounds

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1,2,3-Triazole and its derivatives are an important class of nitrogen containing aromatic heterocyclic compounds and have attracted a great deal of interest due to their diverse biological activities. 1,2,3-Triazoles as attractive linker units which could connect two pharmacophores to give an innovative bifunctional drug, have become increasingly useful and important in constructing bioactive and functional molecules. Triazoles are stable to acidic/basic hydrolysis and also reductive/oxidative conditions, indicative of a high aromatic stabilization. This moiety is relatively resistant to metabolic degradation [1]. 1,2,3-Triazoles are important class of target molecules due to their interesting biological properties such as antitubercular, anti-allergic, anti-bacterial, anti-HIV activity, antifungal, inhibitors of human methionine amino peptidase type 2 (hMetAP2) and α -glycosidase inhibitor. Infectious diseases caused by microorganisms are major concern for human survival accounting for almost 50,000 deaths worldwide daily [2].

Click chemistry is a newer approach for the synthesis of drug like molecules that can accelerate the drug discovery process by utilizing a few practical and reliable reactions. The Cu(I) catalyzed 1,2,3-triazole forming reaction between azides and terminal alkynes has become the gold standard of click chemistry due to its reliability, specificity and biocompatibility. The Cu(I) catalyzed reaction is a mild and very efficient, without protecting groups and purification in many cases. The Cu(I) catalyzed azide alkyne cycloaddition (CuAAC) reaction has successfully fulfilled the requirement of click chemistry as prescribed by Sharpless [3] and within the past few years has become a premier component of synthetic organic chemistry [4]. Since there has been an enormous growth in this area, we restrict this editorial to the methods of synthesis of triazoles, which has been the subject of our attention.

The Cu(I) catalyzed azide-alkyne cycloaddition (CuAAC) reaction is regarded as the jewel in the crown of click chemistry for 1,2,3-triazole synthesis. Sharpless [3] and Meldal [5] groups have reported the dramatic rate enhancement (up to 10^7 times) and improved regioselectivity of the Huisgen 1,3-dipolar cycloaddition reaction of an organic azide and terminal acetylene to afford, regioselectively, the 1,4-disubstituted-1,2,3-triazole in the presence of Cu(I) catalyst.

In click chemistry, standard catalytic system uses Cu (II) salts (e.g., copper sulfate pentahydrate, copper acetate etc.) in presence of a reducing agent, such as sodium ascorbate. For maintaining significantly high levels of the catalytic species, this reducing agent reduces Cu(II) to Cu(I). A mixture of tert-butanol and water is used as solvent, under these conditions it is not necessary to use a base to generate the copper acetylide species. It is important to stress this solvent can also be used for lipophilic compounds. Organic solvents like THF, toluene, DCM, acetonitrile in the presence of stoichiometric amount of copper(I) salts (e.g., CuI, $\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6$, $\text{CuBr}(\text{PPh}_3)_4$ or $\text{CuI}\cdot\text{P}(\text{OEt})_3$) and an excess of a base, usually a tertiary amine (e.g., TEA, DIPEA) can be used. There are number of additives that might increase the efficiency of the reaction, such as the tris-(benzyl-triazolylmethyl)amine (TBTA), triethylamine hydrochloride and the water soluble sulfonated bathopenantroline [6]. The success of the CuAAC highlights the need for selective access to the complementary regioisomers, the 1,5-disubstituted triazoles. 1,5-Disubstituted triazoles can be obtained by a ruthenium catalyzed

“fusion” of organic azides with alkynes. The click-chemistry reaction using $\text{Cp}^*\text{Ru}(\text{PPh}_3)_2\text{Cl}$ as catalyst in benzene to give the 1,5-disubstituted triazoles in good to excellent yields [7]. Boren and co-workers reported a study of $[\text{Cp}^*/\text{RuCl}(\text{PPh}_3)_2]$ and $[\text{Cp}^*/\text{RuCl}(\text{cyclooctadiene})]$ catalysts in the RuAAC synthesis of 1,5-disubstituted-1,2,3-triazoles in toluene at 100 °C [8] and $\text{Ru}(\text{OAc})_2(\text{PPh}_3)_2$ catalyzed 1,4-disubstituted-1,2,3-triazole synthesis [9].

Synthesis of 1,2,3-triazole derivatives using catalytic amount of CuSO_4 and sodium ascorbate in $\text{THF}:\text{H}_2\text{O}$ [10] has been reported. Copper acetate and sodium ascorbate in $\text{CH}_2\text{Cl}_2:\text{H}_2\text{O}$ also used for the synthesis of 1,4-disubstituted-1,2,3-triazole [11]. Similarly, CuI/DBU in toluene [12], NEt_3 , CuI, THF and CuI, NEt_3 in DMSO gave 1,4-disubstituted-1,2,3-triazole derivatives [13]. The CuAAC accelerated by using tris(triazolylmethyl)amine-based ligands. The two new ligands in 3-[4-((bis[(1-tert-butyl-1H-1,2,3-triazol-4-yl)methyl]amino)methyl)-1H-1,2,3-triazol-1-yl]propanol (BTTP) and the corresponding sulfated ligand 3-[4-((bis[(1-tert-butyl-1H-1,2,3-triazol-4-yl)methyl]amino)methyl)-1H-1,2,3-triazol-1-yl]propyl hydrogen sulfate (BTTPS) used for the synthesis of 1,4-disubstituted-1,2,3-triazole [14]. Instead of copper sulphate and reducing agent ascorbic acid, another copper complex $[\text{CuBr}(\text{PPh}_3)_3]$ used in CuAAC reaction at neat or in presence of water at room temperature [15].

At room temperature, the complex $[\text{Tpm}^*\text{BrCu}(\text{NCMe})]\text{BF}_4$ provided the best selectivity in chloroform as the solvent for the synthesis of 1,2,3-triazole [16]. A structurally well-defined copper(I) isonitrile complex is shown to be an efficient, heterogeneous catalyst for the Huisgen azide-alkyne 1,3-dipolar cycloaddition under mild conditions in water [17]. Sulfamoyl azides were subjected to the copper catalyzed azide-alkyne cycloaddition reaction utilizing copper(I) thiophene-2-carboxylate (CuTC) in dry toluene [18], nonbasic anhydrous and aqueous conditions [19]. Synthesis of bistriazoles has been achieved by using tris-(benzyltriazolylmethyl)amine (TBTA), CuI, EtN(i-Pr), in acetonitrile [20].

In addition to Cu(I) catalysts and heterogeneous Cu catalysts, heterogeneous copper catalysts e.g. Cu/Cu₂O nanoparticles, copper in charcoal and copper nanoclusters, $\text{Cu}(\text{OAc})_2$ was reported as a catalyst for the cycloaddition of azides and acetylenes in the absence of sodium ascorbate. CuO(II) nanoparticles in the absence of reductant shows good catalytic activity to form 1,4-disubstituted 1,2,3-triazoles even in wet THF as well as water [21].

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The cycloaddition of a sugar azide with a sugar acetylene (CuI, *i*-Pr₂EtN) was carried out in various ILs as well as in standard molecular solvents (toluene and DMF) to give the 1,4- disubstituted triazole-linked C-disaccharide [22]. In the presence of CuI and *i*-Pr₂EtN in three different ionic liquids, [C₈dabco][N(CN)₂], [C₈dabco][Br] and Ammoeng 110 by thermal and microwave dielectric heating also reported [23]. Efficient and rapid synthesis of 1, 2, 3-triazole derivatives has been achieved *via* Huisgen's 1,3-dipolar cycloaddition between alkyl/arylazides and diethyl/dimethyl acetylenedicarboxylate in excellent yields under solvent-free conditions [24]. The 1,2,3-triazoles were obtained by the Cu(I) catalyzed 1,3-dipolar Huisgen cycloaddition reaction using *t*-BuOH/H₂O as reaction solvents and CuSO₄·5H₂O/sodium ascorbate as the catalyst in ultrasound irradiation [25]. Synthesis of 1,2,3-triazoles by 1,3-dipolar cycloaddition reaction using flow chemistry also reported [26].

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