Organic Chemistry
Current Research
ISSN: 2161-0401

Shaikh et al. Organic Chem Curr Res 2015, 4:2
http://dx.doi.org/10.4172/2161-0401.1000e140

Editorial Open Access

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

Shaikh MH[1], Subhedar DD[1], Danne AB[1], Mane RA[1], Shingare MS[1], Sathe BR[1] and Shingate BB[1*]

[1]Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, 431004, India.

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, regiospecifically, 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, $Cu(CH_3CN)_4PF_6$, CuBr $(PPh_3)_4$ or $CuI{\cdot}P(OEt)_3$) 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 $Cp^*Ru(PPh_3)_2Cl$ 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 $[Cp^*/RuCl(PPh_3)_2]$ and [Cp*/RuCl(cyclooctadiene)] catalysts in the RuAAC synthesis of 1,5-disubstituted-1,2,3-triazoles in toluene at 100 °C [8] and $Ru(OAc)_2(PPh_3)_2$ 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 THF:H_2O [10] has been reported. Copper acetate and sodium ascorbate in CH_2Cl_2:H_2O 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 $[CuBr(PPh_3)_3]$ used in CuAAC reaction at neat or in presence of water at room temperature [15].

At room temperature, the complex $[Tpm^*,BrCu(NCMe)]BF_4$ 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, $EtN(i\text{-}Pr)_2$ in acetonitrile [20].

In addition to Cu(I) catalysts and heterogeneous Cu catalysts, heterogeneous copper catalysts e.g. Cu/Cu_2O nanoparticles, copper in charcoal and copper nanoclusters, $Cu(OAc)_2$ 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].

***Corresponding author:** Shingate BB, Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad 431004, India, Tel: 91-240-2403313; Fax: (91)-240-2403113; E-mail: bapushingate@gmail.com

Received: May 5, 2015; **Accepted:** May 10, 2015; **Published**: June 1, 2015

Citation: Shaikh MH, Subhedar DD, Danne AB, Mane RA, Shingare MS, et al.(2015) Synthetic Strategies for 1,2,3-Triazole Based Bioactive Compounds. Organic Chem Curr Res 4:e140. doi:10.4172/2161-0401.1000e140

The cycloaddition of a sugar azide with a sugar acetylene (CuI, i-Pr_2EtN) 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-Pr_2EtN in three different ionic liquids, [C_8dabco][$N(CN)_2$], [C_8dabco][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/H_2O as reaction solvents and $CuSO_4 5H_2O$/ 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].

References

1. Chrysina D, Bokor E, Alexacou K, Charavgi M, Oikonomakos G, et al. (2009) Amide-1,2,3-triazole bioisosterism: the glycogen phosphorylase case. Asymmetry 20: 733-740.
2. Agalave S, Maujan R, Pore V (2011) Click chemistry 1,2,3-triazoles as pharmacophores. Chem Asian J 6: 2696-2718.
3. Rostovtsev V, Green L, Fokin V, Sharpless K (2002) A stepwise Huisgen cycloaddition process: copper (I)-catalyzed regioselective ligation of azides and terminal alkynes. Angew Chem Int Ed 41: 2596- 2599.
4. Kolb H, Finn M, Sharpless K (2001) Click chemistry diverse chemical function from a few good reactions. Angew Chem Int Ed 40: 2004-2021.
5. Tornoe C, Christensen C, Meldal M (2002) Peptidotriazoles on solid phase: [1,2,3]-triazoles by regiospecific copper(I)-catalyzed 1,3-dipolar cycloadditions of terminal alkynes to azides. J Org Chem 67: 3057-3064.
6. Tron G, Pirali T, Billington R, Canonico P, Sorba G, et al. (2008) Click chemistry reactions in medicinal chemistry: applications of the 1,3-dipolar cycloaddition between azides and alkynes. Med Res Rev 28: 278-308.
7. Imperio D, Pirali T, Galli U, Pagliai F, Cafici L, et al. (2007) Replacement of the lactone moiety on podophyllotoxin and steganacin analogues with a 1,5-disubstituted 1,2,3-triazole via ruthenium-catalyzed click chemistry. Bioorg Med Chem 15: 6748-6757.
8. Boren B, Narayan S, Rasmussen L, Zhang L, Zhao H, et al. (2008) Ruthenium-catalyzed azide-alkyne cycloaddition: scope and mechanism. J Am Chem Soc 130: 8923-8930.
9. Zhang L, Chen X, Xue P, Sun H, Williams I, et al. (2005) Ruthenium-catalyzed cycloaddition of alkynes and organic azides. J Am Chem Soc 127: 15998-15999.
10. Kategaonkar A, Shinde P, Kategaonkar A, Pasale S, Shingate B (2010) Synthesis and biological evaluation of new 2-chloro-3-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)quinoline derivatives via click chemistry approach. Eur J Med Chem 45: 3142-3146.
11. Anjos J, Neves Filho R, do Nascimento S, Srivastava R, de Melo S, et al.(2009) Synthesis and cytotoxic profile of glycosyl-triazole linked to 1,2,4-oxadiazole moiety at C-5 through a straight-chain carbon and oxygen atoms. Eur J Med Chem 44: 3571-3576.
12. Lee S, Hua Y, Park H, Flood AH (2010) Intramolecular hydrogen bonds preorganize an aryl-triazole receptor into a crescent for chloride binding. Org Lett 12: 2100-2102.
13. Doiron J, Soultan A, Richard R, Toure M, Picot N, et al. (2011) Synthesis and structure-activity relationship of 1- and 2-substituted-1,2,3-triazole letrozole-based analogues as aromatase inhibitors. Eur J Med Chem 46: 4010-4024.
14. Wang W, Hong S, Tran A, Jiang H, Triano R, et al. (2011) Sulfated ligands for the copper(I)-catalyzed azide-alkyne cycloaddition. Chem Asian J 6: 2796-2802.
15. Lal S, Gonzalez S (2011) [$CuBr(PPh_3)_3$] for azide-alkyne cycloaddition reactions under strict click conditions. J Org Chem 76: 2367-2373.
16. Cano I, Nicasio M, Perez P (2010) Copper (I) complexes as catalysts for the synthesis of N-sulfonyl-1,2,3-triazoles from N-sulfonylazides and alkynes. Org Biomol Chem 8: 536-538.
17. Liu M, Reiser O (2011) A copper-(I) isonitrile complex as a heterogeneous catalyst for azide-alkyne cycloaddition in water. Org Lett 13: 1102-1105.
18. Culhane J, Fokin V (2011) Synthesis and reactivity of sulfamoyl azides and 1-sulfamoyl-1,2,3-triazoles. Org Lett 13: 4578-4580.
19. Raushel J, Fokin V (2010) Efficient synthesis of 1-sulfonyl-1,2,3-triazoles. Org Lett 12: 4952-4955.
20. Doak B, Scanlon M, Simpson J (2011) Synthesis of unsymmetrical 1,1'-disubstituted bis(1,2,3-triazole)s using monosilylbutadiynes. Org Lett 13: 537-539.
21. Song Y, Yoo C, Hong J, Kim S, Son S, et al. (2008) Nanocrystalline copper oxide(II)-catalyzed alkyne-azide cycloadditions. Bull Korean Chem Soc 29: 1561-1564.
22. Marra A, Vecchi A, Chiappe C, Melai B, Dondoni A , et al. (2008) Validation of the copper(I)-catalyzed azide-alkyne coupling in ionic liquids. Synthesis of a triazole-linked *C*-disaccharide as a case study. J Org Chem 73: 2458-2461.
23. Vecchi A, Melai B, Marra A, Chiappe C, Dondoni A (2008) Microwave-enhanced ionothermal CuAAC for the synthesis of glycoclusters on a calix[4] arene platform. J Org Chem 73: 6437-6440.
24. Shanmugavelan P, Nagarajan S, Sathishkumar M, Ponnuswamy A, Yogeeswari P, et al. (2011) Efficient synthesis and in vitro antitubercular activity of 1,2,3-triazoles as inhibitors of mycobacterium tuberculosis. Bioorg Med Chem Lett 21: 7273-7276.
25. Jiang Y, Chen X, Qua L, Wang J, Yuan J, et al. (2011) Ultrasonic-assisted synthesis of chrysin derivatives linked with 1,2,3-triazoles by 1,3-dipolar cycloaddition reaction. Ultrason Sonochem 18: 527-533.
26. Smith C, Nikbin N, Ley S, Lange H, Baxendale I, et al. (2011) A fully automated, multistep flow synthesis of 5-amino-4-cyano-1,2,3-triazoles. Org Biomol Chem 9: 1938-1947

Citation: Shaikh MH, Subhedar DD, Danne AB, Mane RA, Shingare MS, et al.(2015) Synthetic Strategies for 1,2,3-Triazole Based Bioactive Compounds. Organic Chem Curr Res 4:e140. doi:10.4172/2161-0401.1000e140