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Cu Catalyzed Azide-Alkyne Cycloaddition with Pharmacological Applications of Click Chemistry

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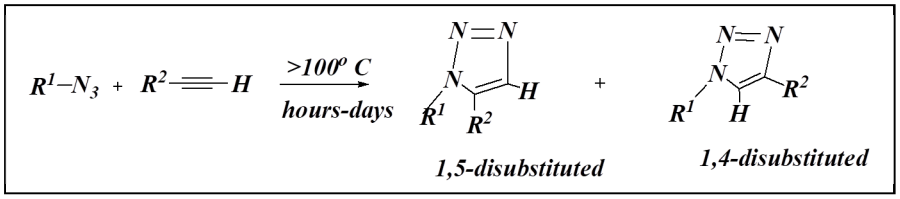
Abstract: ***Click Chemistry concept was introduced by K.B. Sharpless in 2001 which is similar to rapidly assembling of very small building blocks collectively to make a huge structure. "Click" refers to strongly favored, versatile and specific chemical change, which lead to a single reaction product. It is just a term used for a class of reaction that can create very complex molecules in an efficient manner with a higher yield of product. This paper is all about the Cu catalyzed azide-alkyne cycloaddition reaction (CuAAC) leads to the formation of triazoles. It was found that this chemistry uses only the reliable reaction to make complex from electrophiles, olefins and heteroatom linkers. These are found to be high yielding, stereospecific and simple to perform reactions. For these click reactions, the reaction condition should be mild and insensitive to oxygen and water. Cycloaddition of azides and alkyne in the presence of Cu as a catalyst is the most powerful example of click chemistry. The product triazoles formed in the reaction found to exhibit anti-HIV, antibacterial, anticancer activities.***

Keywords: Click Chemistry, Click reaction, Cu catalysed Azide-Alkyne Cycloaddition, Pharmocological application of Click Reaction

I. INTRODUCTION

Click chemistry define by Sharpless [4] as a reaction that is wide in scope, modular, high yielding, produce only harmless byproducts (that can be removed without chromatography), are stereospecific, easy to perform and that require kind or easily removed solvent. The criteria for being classified as click chemistry contain a yield close to 100%., rapidly occurring irreversible, highly selective, use readily available starting material, the stability of new bond. Of all the reactions which achieve click status the Hiusgen 1,3-dipolar cycloaddition of alkynes and azides to yield 1,2,3-triazoles is, without doubt, the ruler example of a click reaction. This reaction was known as the Cream of the crop. The synthesis of 1, 2, 3-triazoles by 1, 3 dipolar cycloadditions was discovered by Micheal at the end of 19th century and considerably advanced by huisgen in the 1960s. The potential of organic azides as the highly energetic yet very selective functional group in organic synthesis and their dipolar cycloaddition with alkenes and alkynes have placed the reaction fulfilling the click criteria. However, the naturally low reaction rate of azide-alkyne cycloaddition did not make it very useful in click context.

II. 1, 3 DIPOLAR CYCLOADDITION OF AZIDES AND ALKYNES



Thermal cycloaddition of azides and alkynes usually require extended heating and results in a mixture of 1, 4 and 1, 5 regioisomers. The activation barrier for the concerted reaction leading to both 1, 4 and 1, 5-regioisomers of the 1, 2, 3-triazole were found to be very close 25.7 and 26.0 kcal/mol. A 1:1 mixture of the two isomers is usually formed in this thermal process.

III. MODIFICATION IN 1, 3-DIPOLAR CYCLODDITION OF AZIDES AND ALKYNES

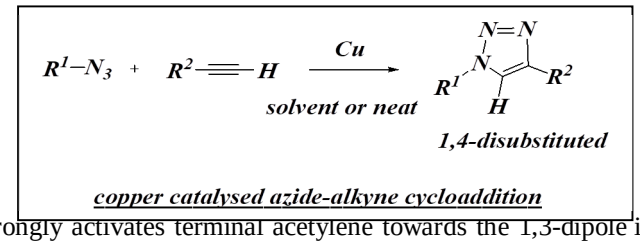
The groups of Sharpless and Meldal discovered the Cu (I)-catalyzed variation of this reaction whose research in this direction has led to its widespread application in all fields of polymer chemistry and biochemistry. This new reaction process requires no protecting groups, and proceed with almost complete conversion and selectively for the 1,4-disubstituted 1,2,3-triazoles(anti-1,2,3-triazole) and also no purification is generally required. So this referred to as 'Click Reaction'.

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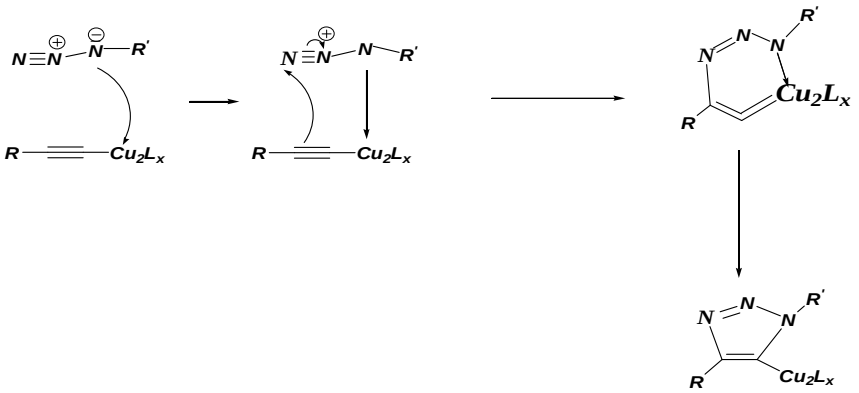
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IV. CU CATALYZED AZIDE–ALKYNE CYCLOADDITION(CUAAC)

The copper-catalyzed Azide-Alkyne Cycloaddition features a huge rate acceleration of 107 to 108 compared to uncatalyzed 1, 3-dipolar Cycloaddition reaction. It succeeds over a broad temperature range, is insensitive to pH range over 4 to 12 and aqueous conditions and tolerates a broad range of functional groups. Pure products can be isolated by simple filtration or extraction without the need for chromatography.



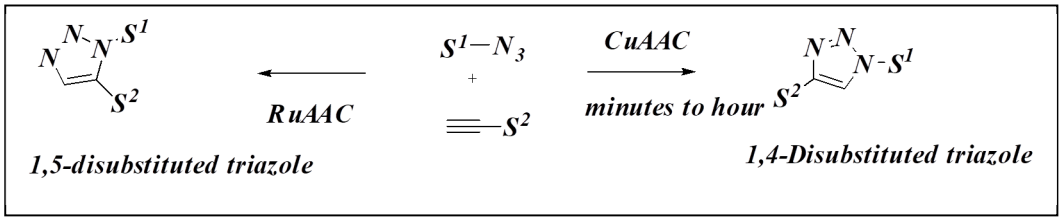
The addition of copper catalyst strongly activates terminal acetylene towards the 1,3-dipole in organic azides. The key C-N bond forming takes place between the nucleophilic, vinylidene like β-carbon of copper(1) acetylide and the electrophilic terminal nitrogen of the coordinated organic azides.



A Simplified representation of the proposed C-N bond making steps in the reaction of copper(I) acetylides with organic azides.

V. REGIOSELECTIVE COMPARISON OF AZIDE-ALKYNE CYCLOADDITION IN DIFFERENT REACTION CATALYTIC CONDITIONS

Ruthenium-catalyzed azide-alkyne cycloaddition reaction form 1,5-disubstituted triazole while Cu catalyzed azide-alkyne cycloaddition reaction form 1,4-disubstituted triazole.



VI. CATALYST AND LIGANDS

The three most common simplistic protocol for click conjugation include direct utilization of a copper(I)source, alternative creation of copper(I) through the reduction of a copper(II) source, and finally oxidation of Cu(I) from the elemental form.The method which employs in situ formation of copper(I) entity using copper(II) salts such as copper sulphate and Cu(OAc)2 is known to be practical because this catalytic system is unaffected by oxidizing as well as aqueous condition, and also provides a high copper(1) concentration through the reaction process. Water is an appropriate choice of solvent for the CuSO4/sodium ascorbate catalyzed click protocol which results in the generation of click inspired triazole product in very high yield and with excellent regioselectivity. A slight excess of ascorbate prevents the formation of the oxidative coupling product that is often observed when a Cu(I) source is used directly. When Cu(I) catalyst is used directly whether by itself or in conjunction with amine ligand, exclusion of oxygen may be required. The use of copper(II) source with the addition of a reducing agent in a large excess has been one of the preferred methods.

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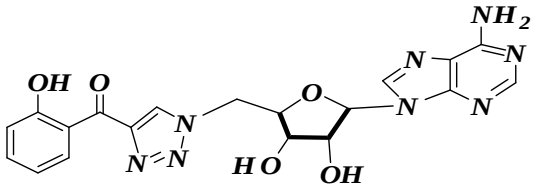
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VII. PHARMACOLOGICAL APPLICATION OF CLICK CHEMISTRY

The triazole scaffolds are found in a number of biologically active compounds exhibiting antibiotics, anti-HIV, antibacterial and antiviral activities. Click chemistry is one of the controlling tools for the production of drug candidates.

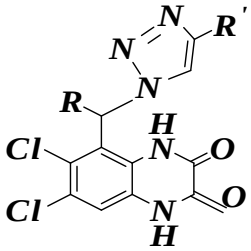
A. Antituberculosis

Tuberculosis(TB) is the most important bacterial cause of infectious disease caused by Mycobacterium tuberculosis, which generally affects the lungs. It is transmitted from person to person through droplets from the esophagus and lungs of people with the active respiratory illness. The current WHO-approved treatment for TB is known as directly observed therapy short-course(DOTS.) involves a three or four-drug regimen comprising isoniazid, rifampin, pyrazinamide and ethambutol for a minimum of 6 months. The emergence of multidrug-resistant tuberculosis demands the development of new drugs.Somu et al reported the compound which was found to be an inhibitor of Mycobacterium tuberculosis. Which was as below:



B. Anticancer

Cancer is the major health burden in both developed and developing countries. Plant-derived agents are being used for the handling of cancer. Several anticancer agents with vinblastine, taxol, the camptothecin derivatives, topotecan and irinotecan, and etoposide are in medical use all over the world. A number of gifted agents such as flavopiridol, roscovitine, combretastatin A-4, betulinic acid and silvestrol are in medical development. However, there is a need to screen new molecules with different modes of action and compound active for other diseases also which may show anticancer activity.M.J. Fray reported a series of 6,7-dichloro-1,4-dihydro-(1H,4H)-quinoxaline-2,3-diones in which the 5-position substituent was a heterocyclylmethyl or 1-(heterocyclyl)-1-propyl group. Most of the compound contains a 1,2,3-triazole ring as the heterocyclic ring. The most influencing compound in the series is 6,7-dichloro-5-[1-(1,2,4-triazole-4-yl)propyl]-1,4-dihydro-(1H,4H)-quinoxaline-2,3- dione.



R=H,CH$_2$CH$_3$etc.
R'=H,n-propyl,CH$_2$NEt$_2$,CH$_2$(1-methylpiperazine)etc.

VIII. CONCLUSION

Cu catalysed azide alkyne cycloaddition is a type of click reaction having approximate 100% yield, wide in scope and highly stereospecific. Here it is concluded that Cu catalysed azide alkyne cycloaddition results in $10^7$to 10^8 times rate acceleration as compared to uncatalyzed azide- alkyne cycloaddition. Cu catalyzed azide alkyne cycloaddition results into stereospecific 1, 4 disubstituted triazole product. It has also a very great application in medicinal chemistry. It exhibit various antibacterial, anti tuberculosis, anti HIV, anticancer activities.

IX. ACKNOWLEDGEMENT

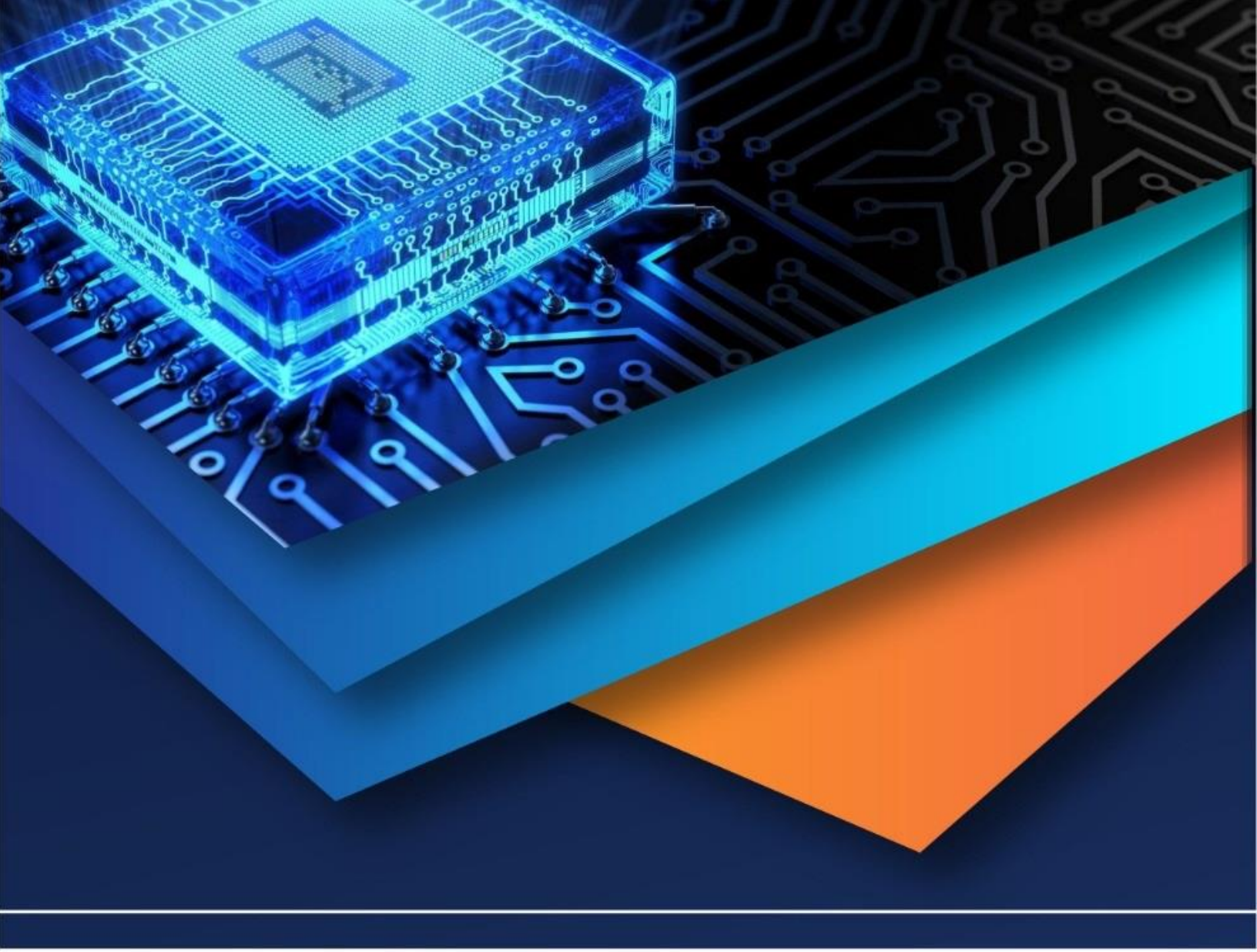
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