

# CLICK REACTION : A NEW APPROACH IN CHEMISTRY

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*Abstract - Click chemistry refers to a class of reactions that are large in scope, easy to perform, fast, easy to purify regiospecific, use of easily available reagents and give high product yields. There are a number of reactions that fulfill the condition of click chemistry but the Huisgen dipolar cycloaddition of terminal alkynes and azides is the ideal example. It has found many applications in research areas, including macromolecular sciences, polymer chemistry, and pharmaceutical sciences. In this script, important aspects of the Huisgen dipolar cycloaddition will be reviewed along with its limitations.*

*Key words: click chemistry, 1,3 dipolar cycloaddition, azides.*

## I. INTRODUCTION

In the field of drug research, researchers are always tried to find new molecules which have some specific properties. While constructing the new molecule actual problem arises with its synthesis and purification. It became easy if already available structures linked together to give the desired structure in few steps.

The concept of click chemistry was put forward by American chemist Dr. K.Barry Sharpless in 2001. Dr. Sharpless defined click chemistry as a group of reactions that should be standard, broad in application, with very high atom economy, generate only harmless byproducts that can be removed by simple methods and stereospecific. It include simple reaction conditions, ideally the process should not be sensitive to oxygen and water, It will perform with easily available starting materials and reagents, most preferentially there is no use of any solvent & if solvent is required water is use as a solvent which can be easily removed, and isolation of product is simple. If Purification required that must be by

simple methods, such as crystallization or distillation, and the product should not be unstable.<sup>4</sup>

The condition for being a click reaction that reaction should give 100% atom economy, fast, irreversible, highly selective. The reaction conditions should be mild, unreactive to oxygen and water and use either no solvents or solvents like water. Protection and deprotection of groups also considered in click reaction to avoid unwanted side reaction. Sometimes water is the ideal reaction solvent providing best yield.

In this review article concept of click chemistry will be discussed, along with its mechanism & limitations.

## II. Classification of Click reaction:

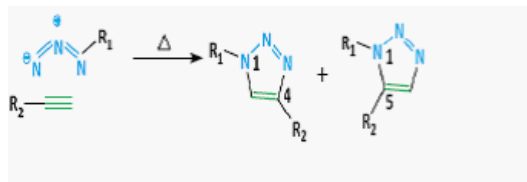
Till date, four major classes of click reactions are as follows:<sup>1</sup>

- Cycloadditions-These preferentially to 1,3-dipolar cycloadditions, but including hetero- Diels-Alder cycloadditions
- Nucleophilic ring-openings-Preferentially strained heterocyclic electrophiles, such as aziridines, epoxides, cyclic sulfates, aziridinium ions, episulfonium ions, etc.
- Carbonyl chemistry of the non-aldol type: Including formations of thioureas, hydrazones, oxime, ureas
- Additions to carbon-carbon multiple bonds-specially oxidation reactions like epoxidation reaction, additions of nitrosyl halide, dihydroxylations, aziridinations, and certain Michael addition.

### III. Cu(I)-CATALYZED HUISGEN 1,3-DIPOLAR CYCLOADDITION OF AZIDES AND TERMINAL ALKYNES

Among all click reactions, Huisgen 1, 3 dipolar cycloaddition of alkyne and azides is an ideal click reaction. Cu(I) catalyzed Huisgen 1, 3 dipolar cycloaddition of alkyne and azides gives 1,2,3 triazole product. It satisfies all the condition of click chemistry therefore widely used. Reaction is a regioselective exclusively forms 1,4 substituted products. It does not require high temperature and can be performed over wide temperature and pH range in variety of solvent with purification of product by filtration. The rate of reaction is  $10^7$  time faster than uncatalyzed cycloaddition.

In the absence of catalyst cycloaddition reaction of azides and alkynes are slow and requires high temperature resulting in the formation of 2 regioisomers that is 1,4 and 1,5 triazol.<sup>2</sup>



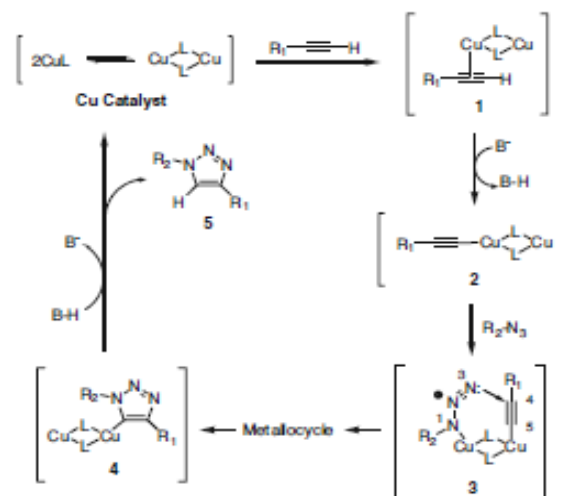
Cu(I) catalyzed Huisgen 1, 3 di polar cycloaddition of alkynes and azides are more popular because it is unaffected by steric factors. Various substituted primary, secondary tertiary and aromatic azides participates in this reaction. Both azides and terminal alkynes are easy to install and are highly stable at standard condition even they can tolerate oxygen, water, organic condition, biological molecules, variety of solvent and large range of pH.

#### IV. Mechanism of HDC reaction

Generally cycloaddition reactions are proceeds through a concerted mechanism but from experimental kinetic data HDC reaction gives evidence that it follows stepwise reaction mechanism.

Depending on experimental proof in the first step of reaction Cu can easily insert in to terminal alkynes to forms pi complex of Cu(I) diamer & alkynes. Then base abstract terminal hydrogen to form Cu acetylide intermediate. In transition state two copper atoms are present. Out of two copper atom one copper atom forms bond with the acetylide intermediate while the other Cu atom require for the activation of the azide. At this stage copper acetylide-azide complex undergoes cyclisation to

form metalocycle. After that acetylide carbon attack on azide group & ring contraction takes place with the dissociation of catalyst which can be regenerated by protonation of the triazole-copper molecule.



(Fig-Huisgen 1,3-dipolar cycloaddition of azides and terminal alkynes)

#### IV. Copper Catalysts

Copper-catalyzed click reactions work only on terminal alkynes. The Cu(I) species either introduced as preformed complexes, or generated in the reaction pot itself by one of the following ways:<sup>3</sup>

- A Cu compound in the +2 oxidation state is added to the reaction in presence of a reducing agent (e.g. sodium ascorbate) which reduces the Cu from the (+2) to the (+1) oxidation state.
- Oxidation of Cu(0) metal
- Halides of copper can be used but it have solubility problem. However, the iodide and bromide Cu salts require either the presence of amines or higher temperatures.

#### V. Limitations of click chemistry:

Till now, in this article we discussed advantages of Cu (I)-catalyzed HDC of terminal alkynes and azides with high yield. However, the HDC reaction has some limitations ,which are discussed below.

• In any cycloaddition, if the energy of diene is low in its ground state then it is not able to interact with a dienophile (the terminal alkynes).

• Many times it may happen that alkynes undergo homocoupling by reacting it with a second alkyne instead of the azide. There are several alkynes homocoupling side reactions that can occur, three of which include Glaser, Straus, and Eglinton couplings

• When CuI-acetylide complex intermediate comes in physical contact with the azide then only click reaction take place, If the CuI-acetylide complex intermediate surrounded by terminal alkynes, then there is a chance of chelate formation

• The molecule should be explosive if the ratio of nitrogen atoms to carbon atoms in an organic molecule is high, or equal to, one

• One major limitation is it requires a copper as a catalyst. The human body requires copper in order to function; excessive intake can cause some side effects like hepatitis, neurological disorders, kidney diseases, and Alzheimer's disease. Therefore, while applying the click reaction in living things it is necessary to remove copper completely which is difficult every time.

• Another problem is biocompatibility of 1,2,3-triazoles. Even though the 1,2,3-triazoles were identified over a century ago there is no generality about their series of actions among molecules in a cell. There are some 1,2,3-triazoles containing compounds which have high toxicities.

• Finally at present, many click-building units and "click products" are not commercially available.

Now it is the responsibility of the pharmaceutical scientist to synthesize compounds which will be available commercially too.

## VI. CONCLUSIONS

Even though all click reactions are easy to use, give high atom economy, fast, regioselective, and are easy to purify, the Cu catalyzed Huisgen 1,3-dipolar cycloaddition of terminal alkynes and azides. It has found number of applications in materials science, polymer chemistry, and the pharmaceutical sciences. Then also HDC reaction is not perfect. There are some important limitations of HDC reaction which are necessarily considered. The most important is it requires a copper catalyst. But high level of copper in the body can lead to serious, even dead

consequences. Other limitations are Cu(I) saturation and alkyne homocoupling. Even all click products are not still commercially available. The stability of some azides may also be a limitation. Though the HDC reaction has some limitations, it is still one of the most versatile and beneficial chemistry tools for pharmaceutical applications. But it is sure that as the industry understands the importance and potential of this reaction and provides all of the basic building blocks; it will grow in popularity and contribute major advances in pharmaceutical sciences and also to other research fields. However as time goes, other click reactions will also find out & give their contribution to chemistry.<sup>7</sup>

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