Click Reaction: A Versatile Field To Chemistry

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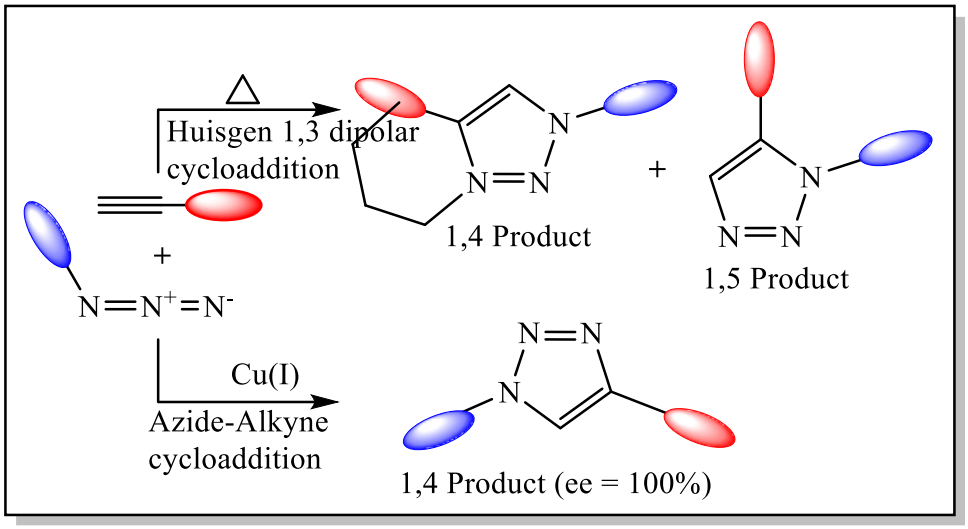
Abstract: This paper is based on the click chemistry basic introduction. Click chemistry has a number of applications in the different fields including medicines, analytical, organic chemistry, organometallic chemistry. It is described here that how it was invented and how it was spread in a very quick time. A lot of importance in all fields.

Keywords: Click Chemistry, Click Reaction

1. Introduction

A click reaction must be modular, wide in scope, high yielding, create only inoffensive by–products (that can be removed without chromatography), are stereospecific, simple to perform and that require benign or easily removed solvent. Click Chemistry was initiated by *K. B. Sharpless, H. C. Kolb and M. G. Finn*, who re–introduced the concept of Huisgen 1,3–dipolar cycloaddition reaction with nearly 100% conversion [1]. Of the reactions embracing the click universe, Huisgen's 1,3-dipolar cycloaddition of alkynes to azides is considered as the "perfect" example of a click reaction that can be dated back to 1960s [2]. The cycloaddition of azides and alkynes to give 1,2,3-triazoles is possibly the most valuable member of this family. Azides and alkynes are the functionalities that are easy to install. Although these are the most energetic species known but still they are among the least reactive functional groups in organic chemistry which is responsible for the slow nature of their cycloaddition reaction and also makes these molecules inert towards biological molecules and environment inside living systems [3]. Thus, the spring-loaded nature of the azide group remains hidden unless a good dipolarophile is present. Even then the triazole forming cycloaddition may require elevated temperatures and usually results in a mixture of 1,4 and 1,5-regioisomers [4].

However, the discovery of azide-alkyne copper catalysed cycloaddition by Meldal and Sharpless has overcome this dilemma and dramatically accelerated the rate of this reaction by regiospecifically uniting azides and terminal alkynes to give only 1,4-disubstituted 1,2,3-triazoles [5]. This unique connection process is simple, appears to have enormous scope and has redefined the concept of click reaction. Copper alkyne-azide cycloaddition (CuAAC) has become the "cream of crop" of click reaction and has found varied applications in drug discovery [6]. Most often, copper(II) salt and a reducing agent is employed as the catalytic system. Instead, metallic copper or Cu clusters can also be employed as catalysts [7] (Scheme 1).

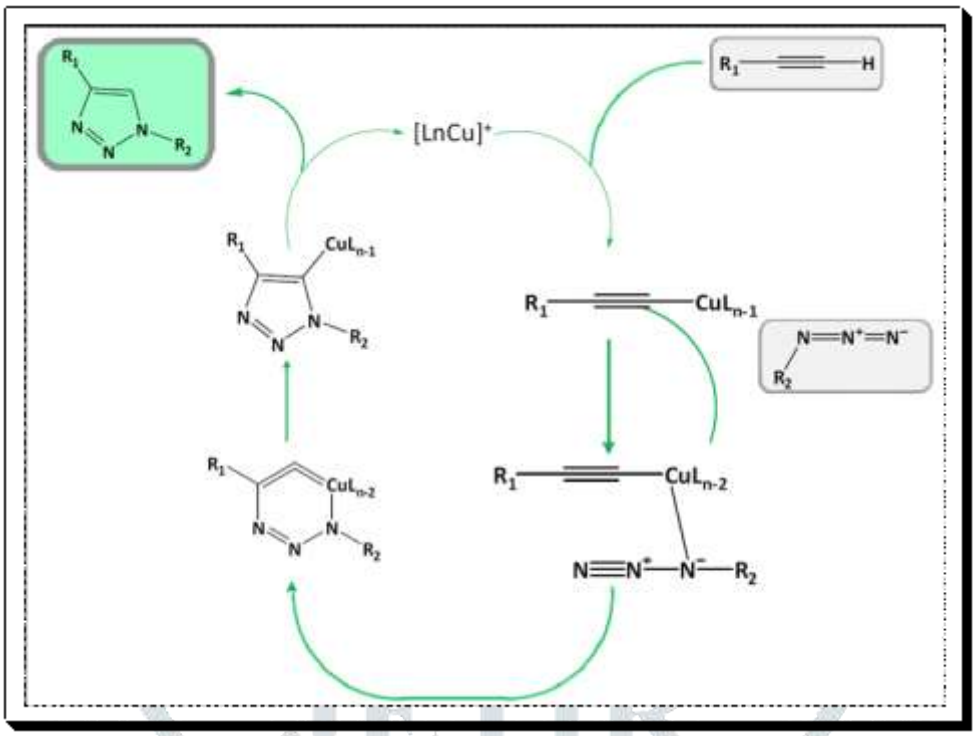


Scheme 1: Huisgen 1, 3 dipolar reaction and modified azide–alkyne cycloaddition reaction

Click chemistry describes tailored chemistry to generate substances efficiently by joining small units together through heteroatom links (C–X–C). It is classified as fast and modular process driven by an approach to irreversible connects substrates involved in click reactions. Click chemistry uses the most reliable reaction conditions to build complex molecules from olefins, electrophiles, and heteroatom linkers. The reaction conditions should be mild, insensitive to oxygen and water and use either no solvents or benign solvents [8]. Click reactions in organic solvents have also a high significance in polymer and material science. Moreover, the bonds generated in the product should be chemically stable under a range of physiological conditions [9].

2. Mechanistic cycle azide–alkyne cycloaddition process

The azide and alkyne groups are kinetically stable under non–catalyzed cycloaddition reactions. But the use of Cu(I) to catalyse this process, under a wide range of conditions such as water, oxygen, different biological molecules or other functionalities present in the reaction efficiently converts azide–alkyne fragments into a 1,2,3–triazolyl heterocycle. The proposed mechanistic cycle [10] for this reaction is shown in (Scheme 2).

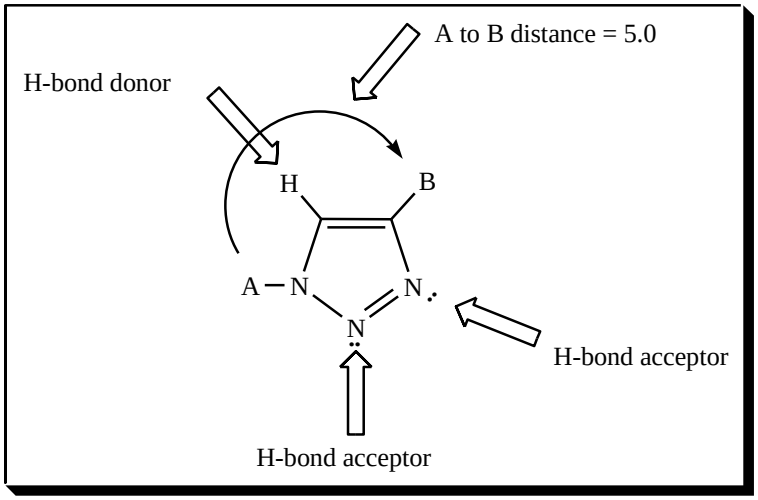


Scheme 2: Mechanistic cycle of Cu(I) assisted azide–alkyne cycloaddition reaction

3. Structural view and significance of triazole segment

1,2,3-Triazole has attracted increasing attention in drug discovery not only because of its ability to act as a rigid linking unit but also because of its favorable physicochemical properties [11]. 1,2,3-triazole core can form π-π interaction with aromatic rings and also possess high dipole moment (5.2-5.6 Debye) that polarizes H-C-5 to such an extent that triazole can act as a weak H-bond donor (Scheme 3). The two nitrogen atoms N-2 and N-3 can form stable H-bonds with hydrogen bond donors and also possess the ability to coordinate with metal ions thus acting as efficient binding unit for recognition of both anions and cations. These interactions favor the binding of triazoles to biomolecular targets and also improve their solubility [12]. 1,2,3-triazole ring can act as a bioisostere of amide moiety resulting in a number of promising antiviral, antibacterial and cytostatic agents with 1,2,3-triazole as an amide surrogate [13]. Moreover, 1,2,3-triazoles being aromatic heterocyclic compounds are also recognized as suitable isosteres of aromatic rings [14], particularly heteroaromatic rings and this ring has also found applications as the isostere of double bond [15]. The importance of 1,2,3–triazolic compounds in medicinal chemistry is undeniable and it mainly contributed in the following activities:

1. HIV Protease Inhibitors
2. Anticancer
3. Antituberculosis
4. Antifungal and Antibacterial



Scheme 3: General structure of triazole

The series of papers by Sharpless *et al.* on use of click chemistry in synthesis of triazole linked substituents with diverse applications of click chemistry in polymer and materials science have been reported. CuAAC reaction has also been successfully used in creating self assembled mono–layers on various surfaces and for creating functional dendrimers [16-21]. Click chemistry has found great applications in fields of pharmaceutical sciences, drug discovery, and syntheses and polymer bio–conjugation [22-29]. As discussed above, the synthetic 1, 2, 3–triazoles show diverse biological activities, such as anticancer, antifungal and antibacterial, antituberculosis, and antivirus. Thus, click chemistry has attracted extensive interest in almost all aspects of drug discovery, such as target–template in vitro chemistry, proteomics and DNA research by using bio–conjugation reactions [30-38].

4. References

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