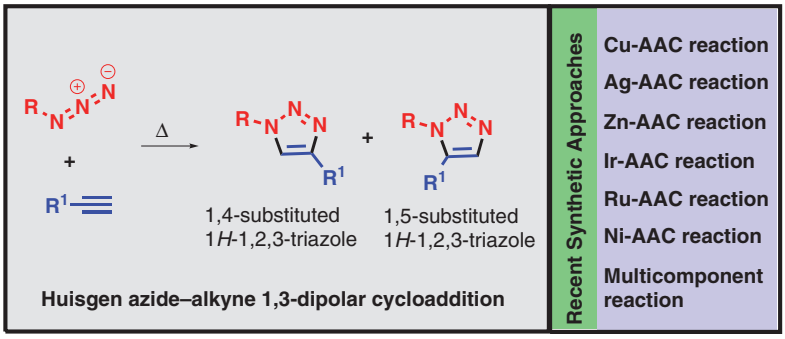
An Overview of Synthetic Approaches towards 1,2,3-Triazoles

Yajat Rohila
Sharol Sebastian
Meenaskhi
Manoj K. Gupta*

Department of Chemistry, School of Basic Sciences, Central University of Haryana, Mahendergarh-123 031, Haryana, India
mkgupta@cuh.ac.in



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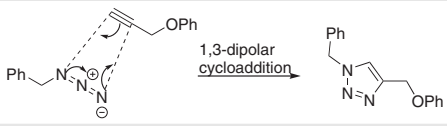
Abstract In this Spotlight article, the authors highlight synthetic methods of 1,2,3-triazoles from 2002 to the present.

Key words triazoles, organic synthesis, azide, alkyne, 1,3-dipolar cycloaddition

Nitrogen-containing heterocyclic compounds, including triazoles, play a crucial role as building blocks for essential biomolecules such as nucleotides, amino acids, and more.[1] Triazoles are five-membered heteroaromatic ring structures with two carbon atoms and three nitrogen atoms, having two isomers: 1,2,3 and 1,2,4. These isomers exhibit a broad range of biological activities, including anticancer, antibacterial, antiviral, anti-inflammatory, antimalarial, and more, making them useful in lead development for drug design and synthesis. With its ease of synthesis in the laboratory, 1,2,3-triazole derivatives have garnered significant attention in the field of organic chemistry.[2] Click chemistry, particularly the Rolf Huisgen cycloaddition reaction[3] continues to be a prominent method for the synthesis of 1,2,3-triazole compounds. Copper-catalyzed and copper-free versions have been developed to minimize toxicity and enhance the reaction's efficiency. These methods have allowed for the synthesis of diverse triazole-containing compounds with applications in medicinal chemistry. Until the late 1960s, the synthetic route towards 1,2,3-triazoles was limited (Scheme 1).[4] But in the late 1970s and early 1980s, after the investigation of the mechanistic approach to this reaction through frontier molecular orbital (FMO) analysis,[5] significant momentum was gained in advancing the synthesis of triazole derivatives. In 2002, Meldal[6] and Sharpless[7] independently worked and subsequently reported their findings on the copper-catalyzed azide and terminal alkyne [3+2] cycloaddition, a reaction that would later become renowned as the 'click reaction'. Further Bertozzi[8] has made significant contributions to bioorthogonal chemistry by developing bioorthogonal reactions that allow for the selective and efficient labeling of biomolecules in complex biological systems, advancing the field of chemical biology and enabling new avenues of research in medicine and diagnostics. In acknowledgement of their pioneering efforts in the field of click chemistry, Morten P. Meldal, K. B. Sharpless, and C. R. Bertozzi were collectively awarded the Nobel Prize in 2022 for the development of 'click' and 'bioorthogonal' chemistry.



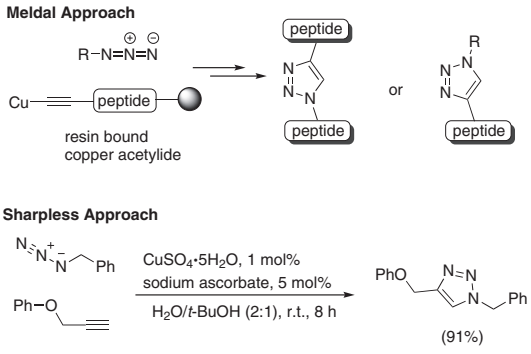
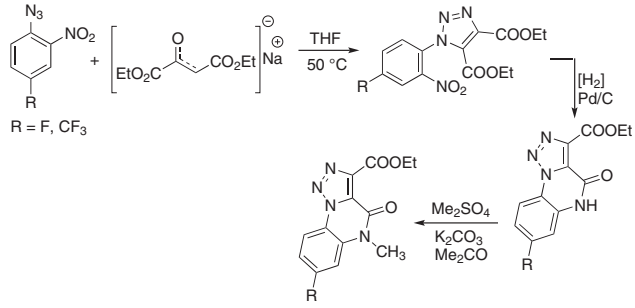
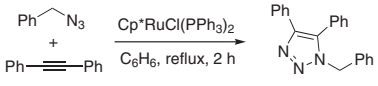
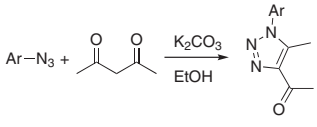
Scheme 1 Huisgen 1,3-dipolar cycloaddition

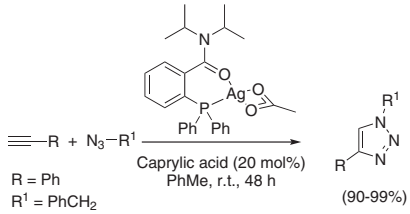
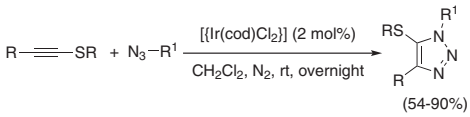
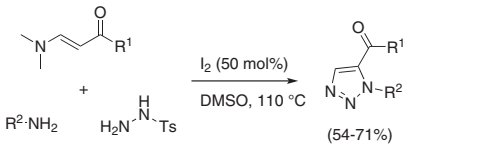
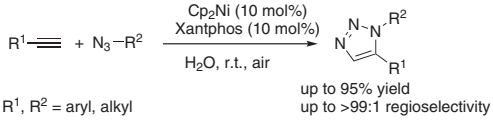
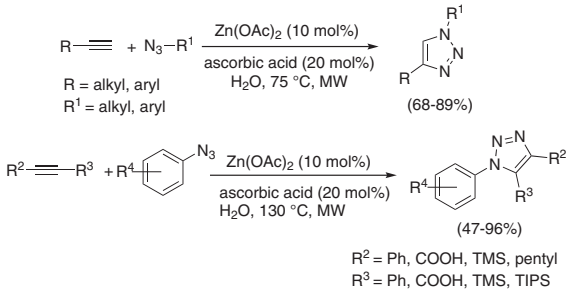
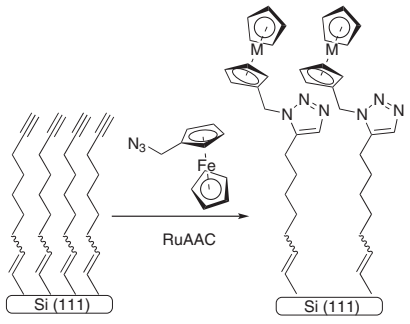
The utilization of click chemistry in the synthesis of 1,2,3-triazoles have facilitated the synthesis of versatile, stable, and biologically compatible compounds. Recent developments in triazole synthesis have delved into copper-free methodologies, including strain-promoted azide–alkyne cycloaddition (SPAAC)[9] and strain-promoted inverse electron-demand Diels–Alder (SPIEDAC)[10] reactions. These approaches help mitigate the risk of copper-induced toxicity in biological applications.

This article provides an in-depth exploration of the evolution of 1,2,3-triazoles from 2002 to the present, emphasizing their synthesis, advantages, and burgeoning signifi-

cance in biological applications (Table 1). The methodology discussed facilitates the incorporation of 1,2,3-triazole units into diverse compounds, forming the basis for bioconjugation strategies and the synthesis of druglike molecules. The relevance of this approach is underscored by the fact that several established drugs, including carboxyamidotriazole, IA-09, cefatrizine, tazobactam, ravuconazole, rufinamide, fluconazole, ribavirin, mubritinib, itraconazole, TSAO-46, voriconazole, posaconazole, among others,[11] are derived from 1,2,3-triazoles. These triazoles are intricately linked with diverse heterocyclic components, exhibiting a spectrum of biological activities such as anticancer,[12] antimicrobial,[13] anti-inflammatory,[14] antifungal,[15] antibacterial,[16] antitubercular,[17] and antiviral properties.[18] This evidence strongly supports the proposition that the combination of triazoles with various heterocyclic components is poised to enhance biological efficacy, thereby making substantial contributions to the pharmaceutical and drug industry.

Table 1 Different Methods for the Synthesis of 1,2,3-Triazoles

(A) In 2002, Meldal and coworkers[6] disclosed a synthetic pathway involving a novel regiospecific copper(I)-catalyzed 1,3-dipolar cycloaddition of terminal alkynes to azides on a solid phase. This method enabled the synthesis of 1*H*-[1,2,3]-triazoles using primary, secondary, and tertiary alkyl azides, aryl azides, and an azido sugar, yielding the corresponding 1,4-disubstituted 1,2,3-triazoles in peptide backbones or side chains with a conversion rate exceeding 95%. Similarly, Sharpless and co-workers[7] employed a stepwise Huisgen cycloaddition process to create a ligation of azides and terminal alkynes through copper(I)-catalyzed reactions. This approach yielded regioselective 1,4-disubstituted 1,2,3-triazoles by employing phenyl propargyl ether and benzyl azide, achieving an excellent yield under ambient conditions. These methods offer several advantages including high regioselectivity, a broad spectrum of substrate compatibility, enhanced atom efficiency, and the generation of synthesized compounds with high yields. Subsequently, this reaction gained widespread recognition as the copper(I)-catalyzed alkyne–azide cycloaddition (CuAAC) reaction. These ground-breaking methods laid the foundation for click chemistry, a potent synthetic approach facilitating efficient and selective molecular assembly. Click chemistry has witnessed extensive applications in drug development, materials science, and bioconjugation, revolutionizing research across various fields by streamlining the synthesis of functional molecules and materials with precision and simplicity.	
(B) In 2002, Biagi et al.[19] customized a novel set of 1,2,3-triazolo[1,5-*a*]quinoxalines and investigated their binding affinity in benzodiazepine and adenosine receptors. The synthesis method employed diethyl oxalacetate sodium salt and 1-azido-2-nitrobenzene derivatives, enabling the production of these compounds at 50 °C.	
(C) In 2005, Zgang et al.[20] devised a highly effective method for the synthesis of 1,5-disubstituted triazoles, utilizing ruthenium as a catalyst. This process demonstrated efficacy in generating fully substituted 1,2,3-triazoles through the use of internal alkynes. A significant advantage of this method lies in the formation of 1,5-disubstituted 1,2,3-triazoles. Subsequently, this reaction became recognized as the ruthenium-catalyzed azide–alkyne reaction (RuAAC).	
(D) In 2008, Kannan and coworkers[21] introduced a synthetic method for preparing 4-acetyl-5-methyl-1,2,3-triazoles utilizing acetylacetone and aromatic azides. This approach encompasses a 1,3-dipolar cycloaddition reaction involving the azide and acetylacetone in the presence of a base, conducted in ethanol solvent at higher temperatures, yielding 1,4-regioisomers of 1,2,3-triazoles.	

(E) McNulty et al.[22] formulated a technique for the regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles utilizing a silver(I) complex. They devised a distinctive silver(I)acetate complex linked to a 2-diphenylphosphine-*N*,*N*-diisopropyl carboxamide ligand, unveiling the first report of silver azide–alkyne cycloaddition (Ag-AAC) reaction. Control experiments showed that the reaction progressed through the formation of silver acetylide, but that cyclization required additional activation of the acetylide–azide intermediate. Notably, this method offers the advantage of regioselectivity and is conducted under mild reaction conditions.	
(F) Sun and his coworkers[23] introduced an innovative intramolecular reaction wherein azide and alkyne were catalyzed by iridium, giving rise to what is now recognized as IrAAC (iridium-catalyzed alkyne–azide cycloaddition). This methodology allows for the utilization of internal alkynes and stands out as the first efficient intermolecular AAC of internal thioalkynes. The reaction exhibits notable features, including high efficiency, moderate reaction conditions, regioselectivity, ease of operation, compatibility with a broad range of organic and aqueous solvents, as well as air. Notably, it complements the well-established CuAAC and RuAAC reactions.	
(G) Wan et al.[24] devised a metal-free and azide-free approach based on enaminone three-component synthesis to produce 1,5-disubstituted 1,2,3-triazoles. The method involved various amines, tosyl hydrazine, and enamines in an iodine-mediated environment. The reaction encompassed a cascade of dual C–N, N–N bond formation, and an acyl migration driven C–C bonding process in three-component reactions involving enaminones, tosyl hydrazine, and primary amines. Notably, this regioselective synthesis technique relied solely on molecular iodine and did not involve oxidants. This method holds promise as an alternative to classical approaches for synthesizing 1,2,3-triazoles.	
(H) Kim et al.[25] innovated a catalytic method employing Cp_2Ni/Xantphos to produce 1,5-disubstituted 1,2,3-triazoles under gentle reaction conditions. This process is amenable to both water and organic solvents, exhibiting a broad substrate scope that encompasses both aliphatic and aromatic substrates. The protocol is user-friendly and scalable, making it applicable for synthesizing triazoles linked to carbohydrates or amino acids.	
(I) Morozova et al.[26] devised a $Zn(OAc)_2$-catalyzed alkyne-azide cycloaddition reaction for the preparation of 1,4-disubstituted 1,2,3-triazoles. This pioneering method of azide-alkyne cycloaddition (AAC) conducted in water utilizes $Zn(OAc)_2$ as an affordable and environmentally friendly catalyst. The approach was applied to synthesize both 1,4-disubstituted 1,2,3-triazoles using terminal alkynes and 1,4,5-trisubstituted 1,2,3-triazoles using internal alkynes. The Zn-catalyzed AAC reaction exhibits sensitivity to steric hindrance in acetylenes, leading to the development of a regioselective approach to triazole synthesis.	
(K) In a recent study, Li et al.[27] illustrated the viability of the RuAAC reaction as a surface chemical process and provided evidence that the catalyst's size influences the reaction kinetics. The researchers conducted a hydrosilylation reaction between oxide-free silicon (Si–H) electrodes and 1,8-nonadiyne, followed by treatment with ruthenium as a catalyst to yield the 1,5-isomer of 1,2,3-triazoles.	

Multicomponent reactions have gained popularity for their efficiency in generating complex molecules.[28] Isocyanides, amines, and azides are commonly used components in MCRs to produce 1,2,3-triazoles. The Ugi reaction,[29] Passerini reaction,[30] and many other MCRs have been adapted for the synthesis of triazole hybrids, enabling the rapid gen-

eration of diverse compound libraries. Bioorthogonal reactions that are compatible with living systems have been explored for the synthesis of 1,2,3-triazole hybrids. Copper-free click chemistry and strain-promoted azide–alkyne cycloadditions (SPAAC) have been used to introduce triazole moieties into biomolecules for applications in chemical biology, bioconjugation, and drug delivery. Microwave-assisted synthesis[31] has become an attractive method for the rapid generation of 1,2,3-triazole hybrids. This approach offers shorter reaction times, improved yields, and reduced environmental impact. Researchers have employed microwave irradiation to accelerate traditional click reactions and other triazole-forming reactions. Solid-phase synthesis also has gained momentum in the synthesis of triazole-based compounds, particularly for high-throughput screening in drug discovery. This approach enables the efficient synthesis of compound libraries by immobilizing reactants on solid supports, facilitating purification and characterization. Researchers have designed cascade reactions to streamline the synthesis of 1,2,3-triazole hybrids. These one-pot processes involve multiple reactions occurring sequentially, resulting in complex molecules in a single operation. Cascade reactions reduce the number of reaction steps and waste production. Further enzymatic methods[32] have also been explored for the synthesis of 1,2,3-triazoles. Enzymes like azide–alkyne cycloaddases and transketolases have been used to catalyze the formation of triazoles, providing green and selective routes for their preparation. With increasing emphasis on sustainable chemistry, researchers have developed environmentally friendly methods for triazole synthesis. Green solvents, biobased starting materials, and alternative energy sources have been integrated to reduce the environmental impact of these syntheses. Achieving regioselectivity and stereoselectivity in triazole synthesis remains a challenge. However, recent advances in catalyst design and reaction conditions have led to improved control over the regioselective and stereoselective aspects of the synthesis. The use of click chemistry, multicomponent reactions, bioorthogonal chemistry, and innovative techniques like microwave-assisted and solid-phase synthesis[33] have enabled the rapid generation of diverse triazole-containing compounds. Moreover, the application of these compounds in drug discovery, chemical biology, and materials science continues to expand, making this area of research highly promising for the future prospects. Recent advancements in technology and equipment have enhanced the synthesis of triazoles, resulting in improved yields, enhanced atom economy, and adherence to green chemistry principles.[34] Several recent reports have demonstrated the successful synthesis of triazoles through ultrasound-assisted process.

In this Spotlight article, we have summarized the various methods known for the synthesis of 1,2,3-triazoles. The synthesis of 1,2,3-triazole holds promising prospects in various fields, particularly in pharmaceuticals, materials science, and chemical biology. Green chemistry principles will play a crucial role in developing more sustainable and environmentally friendly methods for 1,2,3-triazole synthesis. In addition to this, sustainability will be enhanced by reduction in waste and usage of renewable feedstocks to create these pharmaceutically important compounds. It is envisioned that a comprehensive review on such compounds will continue to be in central core of click chemistry reactions, facilitating the rapid construction of complex molecules and bioconjugates for drug discovery and materials science applications. It will remain valuable in bioorthogonal reactions for labeling and probing biomolecules, aiding in the elucidation of cellular processes. Triazoles will continue to be key components in drug design, with researchers exploring their potential in targeting various diseases, including cancer, infectious diseases, and neurological disorders. The versatility of 1,2,3-triazoles will lead to innovative materials with tailored properties such as conducting polymers, molecular sensors, and advanced coatings. In forthcoming years, the synthesis of 1,2,3-triazoles will evolve more towards sustainability, efficient processes and their applications in drug development and lead formation for various diseases.

Conflict of Interest

The authors declare no conflict of interest.

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