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Research Article

Synthetic Trends Followed for the Development of 1,2,3-Triazole Derivatives

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Abstract

1,2,3-triazoles find their application in the diverse areas of medicine. Enough literature is available demonstrating antibacterial, antifungal, anticonvulsant, antiviral, antidiabetic and antimalarial potential. Owing to their wide application, scientists across the globe are engaged in the design and development of 1,2,3-triazole based medicinal agents. However, the approach for development of such agents involving Huisgen's cycloaddition reaction has gained immense importance. This manuscript covers different conventional and non-conventional approaches adopted for the synthesis of 1,2,3-triazole derivatives.

Keywords: Triazole; Synthesis; 1,2,3-Triazole

Introduction

Triazoles, five-membered heterocyclic compounds, with molecular formula $C_2H_3N_3$, bearing three nitrogen atoms in the ring exist in two isomeric forms namely 1,2,3-triazoles and 1,2,4-triazoles [1,2] (Figure 1). Due to higher aromatic stabilization of 1,2,3-triazoles, they are resistant to oxidation, reduction, and hydrolysis in both acidic ad basic conditions. Their active participation in hydrogen bond formation, dipole-dipole and pi stacking interactions enhance their binding ability with different biological targets [3].

Over the past decade, scientists across the globe have shown substantial interest in the synthesis of 1,2,3-triazole units [4]. This moiety can be found in a number of pharmaceutical agents as shown in Figure 2. Tazobactam, a α-lactamase inhibitor, contains this moiety [5]. Cefatriazine, an orally active semisynthetic cephalosporin antibiotic [6] and rufinamide, an anticonvulsant agent bear 1,2,3-triazole [7]. This moiety finds several applications in the medical field such as antitubercular [8], antibacterial, antifungal [9], anticancer, antioxidant [10], antimalarial [11], antidiabetic [12] etc.

Huisgen was the very first one to study the synthesis of 1,2,3-triazoles, naming it as Huisgen 1,3-dipolar cycloaddition. This reaction mechanism involves reaction of an alkyne with an azide to produce 1,4- and 1,5-disubstituted-triazole derivatives [13]. Further, in order to regioselectivity, different methodologies were developed. It was seen that copper catalyzed cycloaddition reaction led to the formation of 1,4-regioisomer whereas, 1,5-regiomer was formed in the presence of ruthenium. Products obtained from all these conditions have been shown in Figure 3 [14-16]. However, application of Cu-AAC is most commonly used employed in the synthesis as evident from the literature [17,18].

Methodology for Synthesis

Synthesis using metals

Copper catalyzed 1,3-dipolar cycloaddition: Copper caltalyzed 1,3-dipolar cycloaddition reaction between an alkyne and azide (Cu-AAC) is the most commonly employed method for the synthesis of 1,2,3-triazoles [19,20]. General conditions for cycloaddition include the presence of Cu(I) or Cu(II) salts along with a reducing agent in some organic solvent or a mixture of water and tert-butyl alcohol at room temperature [21,22]. Zheng and Shi reported a Cu-catalyzed route taking N-tosylhydrazones and azides as the substrates [23]. Chen and co-workers have also demonstrated 1,2,3-triazoles synthesis from N-tosylhydrazones and anilines [24]. An overview of these routes is provided in Figure 4.

Ruthenium catalyzed reactions: Ruthenium catalysts are most widely employed for the preparation of 1,5-disubstituted triazoles from azide and alkyne. However, this method suffers from the drawback that this is not efficient in case of sterically demanding substrates, leading to the formation of by-products. Ferrini et al. have reported ruthenium-catalyzed synthesis of 5-amino-1,2,3-triazoles [25]. Ruthenium(II) carboxylate complexes were used for efficient cross-dehydrogenative alkenylations of N-aryl-1,2,3-triazoles [26]. These routes have been shown in Figure 5.

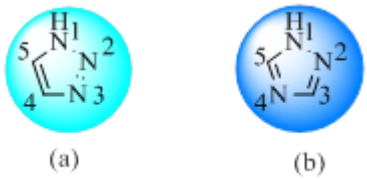

Figure 1: Isomers of triazole (a) 1,2,3-triazole (b) 1,2,3-triazole.

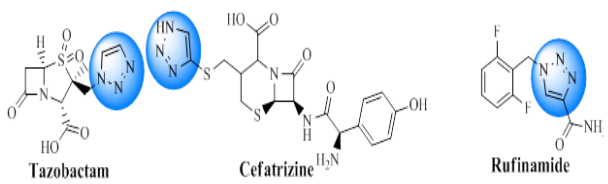

Figure 2: 1,2,3-Triazole bearing drugs.

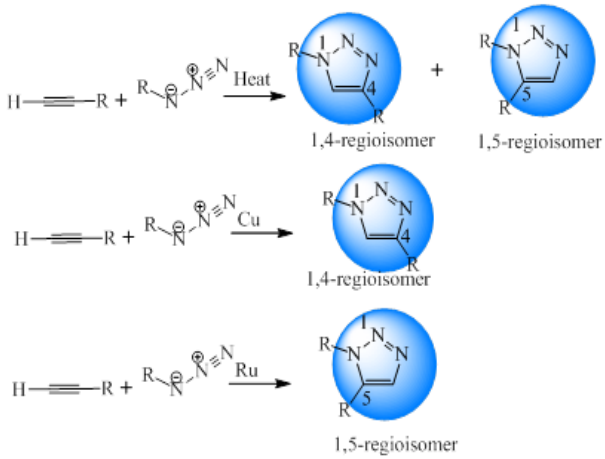

Figure 3: Regioselectivity under different reaction conditions.

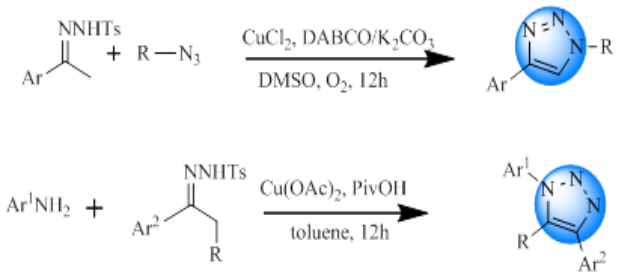

Figure 4: Copper catalyzed synthesis of 1,2,3-triazole.

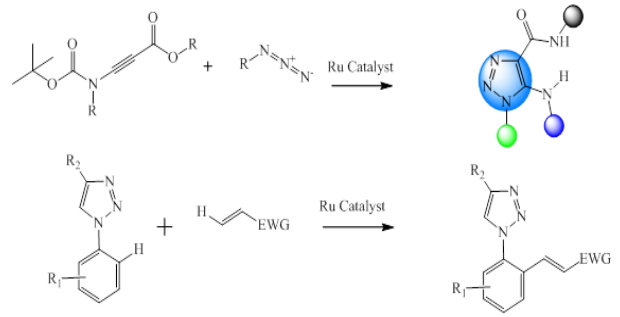

Figure 5: Reaction routes using ruthenium catalyst.

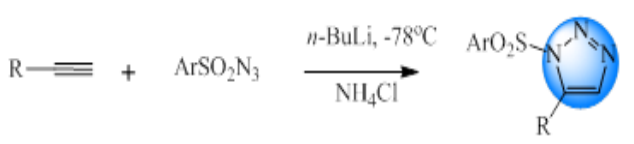

Figure 6: Lithium Catalyzed Reaction.

Lithium catalyzed reactions: Meza-Avina et al. reported the reaction between acetylides and sulfonyl azides for the formation of selective 1,5-substituted sulfonyl triazoles. This sort of reaction provided regioisomeric product in comparison to the conventional copper-catalysed azide-alkyne cycloaddition [27]. Overview of this reaction is given in Figures 6 and 7.

Zinc mediated synthesis: Smith and Greaney performed zinc mediated ligation of azide-alkyne to form 1,5- and 1,4,5-substituted 1,2,3-triazoles. Reactions were carried out at room temperature [28].

Metal-less reactions

In an attempt to develop method for synthesis of 1,2,3-triazoles without using metals, they synthesized 1,5-disubstituted 1,2,3-triazoles using primary amines, enolizable ketones and 4-nitrophenyl azide [29]. Kwok et al. adopted a synthetic route for synthesis of 1,5-diarylsubstituted 1,2,3-triazoles from azides and terminal alkynes in DMSO in the presence of catalytic tetraalkylammonium hydroxide [30]. Bonacorso and co-workers reported synthesis of antiepileptic drug, rufinamide in the absence of any solvent, metal catalyst and reducing agent. Desired product was obtained in good yields [31]. Singh et al. developed a metal free route for development of 1,2,3-triazoles. [3+2] cycloaddition of aryl azides with activated cyclic C-H acids was brought about in the presence of DBU [32]. Jia et al. carried out 1,3-dipolar cycloaddition of commercially available aldehydes with azides and secondary amines in the absence of metal catalyst [33]. Overview of all routes is given in Figure 8.

Ultrasound-assisted synthesis

Silva et al. reported synthesis of twelve isatin derivatives in the presence of different alkynes and ultrasound irradiation. Better yields and less time consumption were advantages over the conventional methods [34]. Triazole derivatives were obtained via 1,3-dipolar cycloaddition reaction between 2-azido-N-(benzo[d]thiazol-2-yl) acetamide derivatives and different alkynes in the presence of ultrasound radiation. Reaction was carried out in solvent system comprising of t-BuOH/H_2O (1:1 v/v) with $CuSO_4.5H_2O$ as the catalyst [35]. 1,2,3-triazoles as PDE4 inhibitors were prepared by CuAAC method under ultrasound irradiation at room temperature [36]. CuAAC was employed to catalyze the reaction to obtain a series of 1,2,3-triazoles in benign solvents under ultrasound irradiation. Sonication served the benefits of reduced reaction time and better yields [37]. Zhang and co-workers reported an efficient synthesis of 1,2,3-triazole derivatives via 1,3-dipolar cycloaddition using copper acetate and sodium ascorbate as catalyst under ultrasonic radiation [38]. Overview of these reactions is given in Figure 9.

Microwave assisted reactions

Microwave assisted synthesis of triazoles is well studied. Microwave irradiation allows efficient internal heat transfer, which reduces the reaction timing as well as elevates the reaction rate and yield [39]. Costa et al. reported microwave assisted synthesis of 1,2,3-trizole derivatives via 1,3-dipolar cycloaddition as anticancer agents. Souza and co-workers also synthesized novel triazoles based on a microwave-assisted multicomponent reaction [40]. Such reactions have been shown in Figure 10.

Conclusion

1,2,3-triazoles find their significant place in the field of drug discovery and development. This drives the interest of different scientists for development of novel methods for synthesis of 1,2,3-triazole derivatives. Different conventional methods, i.e., with metal or without metal employed in this way have been reported. A few alternative methods like ultrasonic or microwave irradiation have also been included.

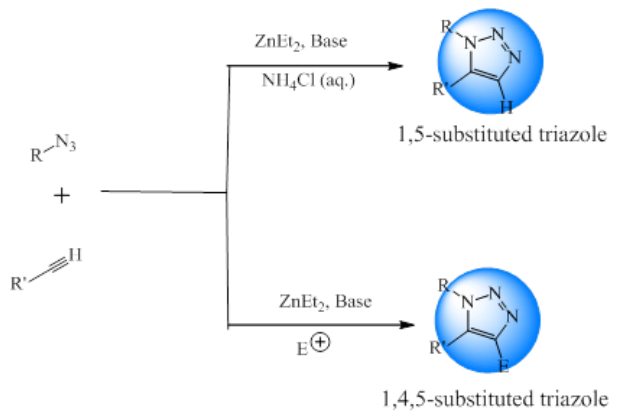

Figure 7: Zinc mediated reaction of 1,2,3-triazole.

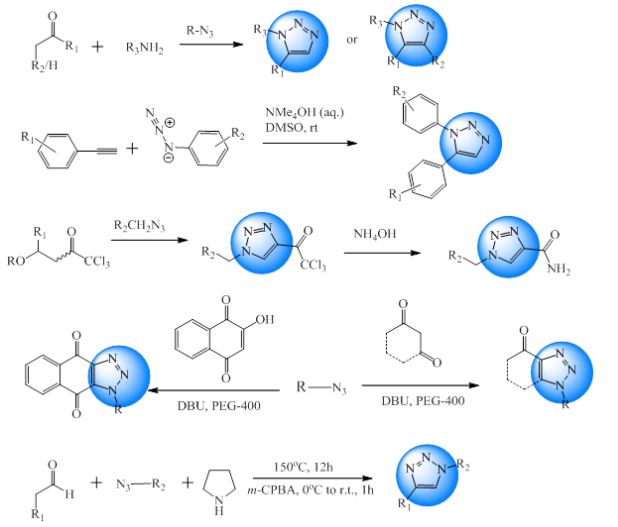

Figure 8: Metal-free synthetic routes for synthesis of 1,2,3-triazole derivatives.

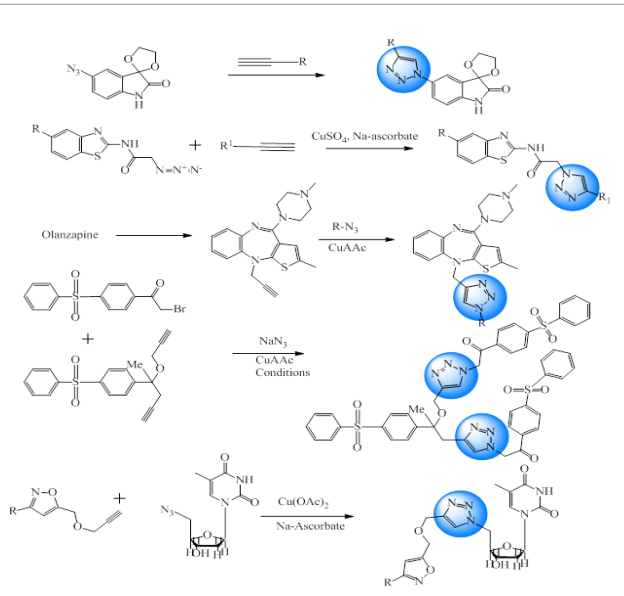

Figure 9: Ultrasonics assisted reactions.

Figure 10: Microwave assisted synthesis of triazoles.

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