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1,2,3-Triazoles as Molecular Scaffolds for Biomedical and Biomolecular Mimetics: Synthesis and Reactions of 1,2,3-Triazoles

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Abstract

Since the beginning of applying click chemistry in synthetic chemistry; 1,2,3-triazoles has gained a great interest from medicinal chemists. Recently, 1,2,3-has been at the center of modern biomedical and organic chemistry as well. Their distinguished framework has revealed broad applications in drug discovery, pharmacology, organic synthesis, chemical biology, fluorescent imaging, polymer chemistry, material science and bioconjugates. Owing to their great importance and versatile applications in different fields, synthesis of I,2,3-triazoles utilizing available chemicals is more desirable. This review illustrated different conventional and non-conventional approaches for synthesis and reactions of this important moiety.

Keywords: 1,2,3-Triazoles; click chemistry;1,3-dipolar cycloaddition; Huisgen reactions; Alkylation; Acylation; Triazole synthesis; Triazole Reactions.

1. Introduction

1,2,3-triazoles are of the most important nitrogenous heterocyclic ring systems. They possess pharmaceutical and therapeutic values [1–6]. They act as anticancer agents, synthetic intermediates for antibiotic, chemiluminescent compounds, GABA-antagonists, muscarinic agonists for treatment of Alzheimer's disease[7,8], antihistaminic agents, nucleosides, rotaxanes, and polyheterocyclic compounds with neuroleptic activity[9–11]. They have many applications industrially also as plant growth regulator, insecticides, corrosion inhibitors, fungicides, optical brighteners, photostabilizers for plastics, fibers, dyes, and uv-screens for protection of the skin[12].

The biochemical and pharmaceutical importance of 1,2,3-triazoles lies in the fact they can be used effectively as 5α-reductase inhibitors, c-Met kinase inhibitors, aromatase inhibitors[13–16], antibacterial agents[17,18], novel H1V inhibitors, glycosidase inhibitors and antimalarial agents[19]. The most common potential drugs based on 1,2,3-triazoles include the anticancer drug CAI, TSAO, Tazobactum and Cetirizine (**Figure 1**).

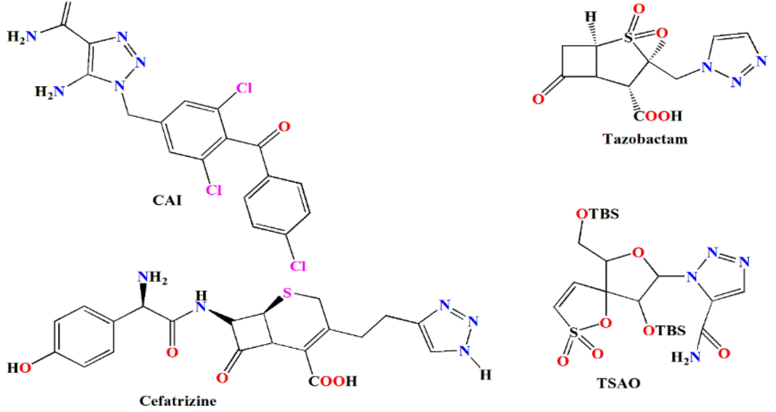

Figure1: Structures of The Most Common Potential Drugs Based on 1,2,3-Triazoles

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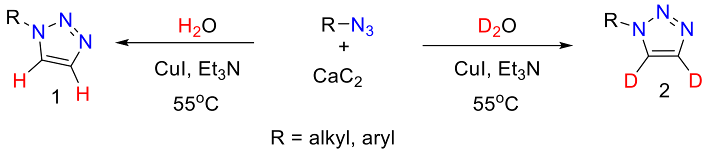
Owing to the high local denisity of nitrogen atoms; macromolecules with poly-1,2,3-triazoles, which synthesized through 1,3-dipolar cycloaddition of polyazides to acetylenedicarboxylic esters, they can be utilized for the complexation of metal ions.

1. Synthesis of 1,2,3-Triazoles

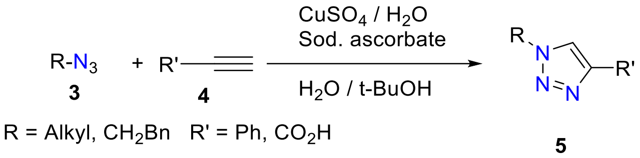
1.1. From Alkyl or Aryl Azides

Jiang et al. first reported the utility of calcium carbide as a source of acetylene to synthesize 1,2,3- triazoles[6,20–22]. (**Scheme 1**).



Scheme 1

Alkynes were submitted to react with azides in the presence of catalyst prepared in situ via the reduction of $CuSO_4$ with sodium ascorbate or/and ascorbic acid. The reaction performed in 6-36 hrs. at RT in a different solvent (aqueous tert-butyl alcohol/water)[23–25] (**Scheme 2**).

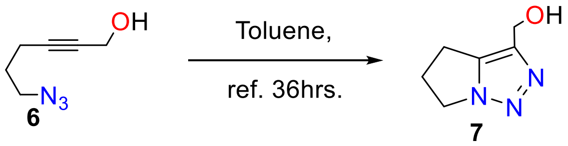


Scheme 2

1.1. Intramolecular 1,3-Dipolar Cycloadditions[26]

Polycyclic triazoles were prepared through the 1,3-dipolar interamolecular cycloaddition of an azido group onto acetylene group. Azides **6**, as authentic sample, afford triazole **7** (52%), when heated under reflux in toluene (**Scheme 3**).

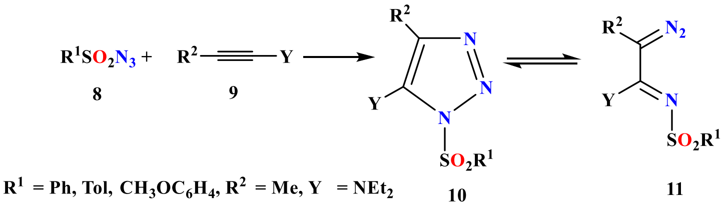
Another important development the microwave assisted 1,3-dipolar cycloaddition of azides to alkynes without using of solvent. Green synthesis has many advantages over the traditional methods; low coast, reduced pollution and substantial decrease in the reaction time[26,27].



Scheme 3

1.2. From Sulfonyl Azides

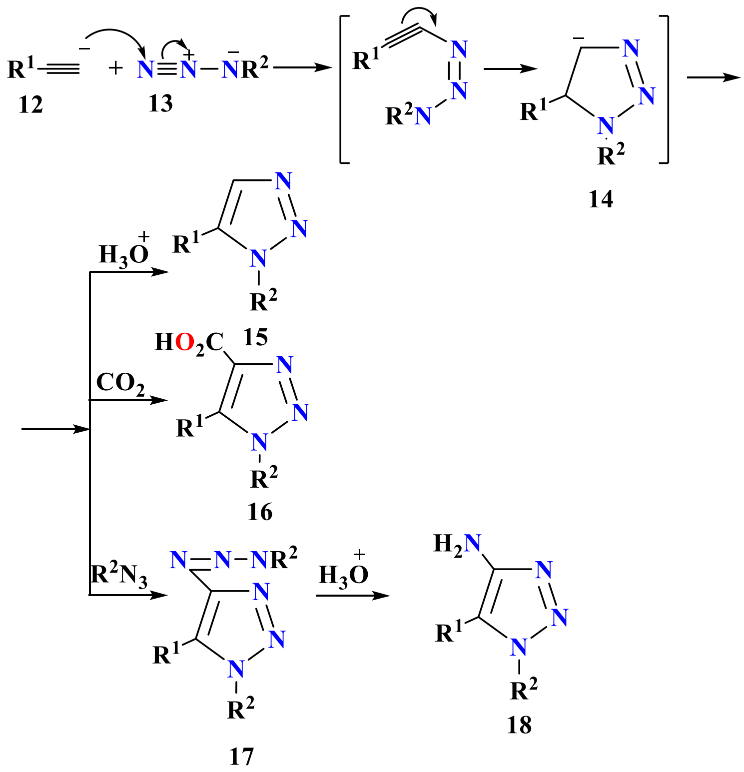
Sulfonyl azides **8** undergo addition to electron-rich alkynes **9** to give 1-sulfonyl-1H-1,2,3-triazoles**10** which in solution, exist in equilibrium with open-chain diazotautomers[28]. (**Scheme 4**).



Scheme 4

1.3. From Sulfonyl Azide with Metal Acetylids [29,30]

Lithium, magnesium and sodium terminal alkynes derivatives with ary, alkyl and sulfonyl azides afforded triazoles. The required condition for this reaction (0^0C or less) revealed that the mechanism of the reaction different completely from the normal adsition of azide to alkynes. The reaction involved nucleophilic attack on the terminal nitrogen of the azide by the anion **12** followed by 1,5-anionic cyclization to afford the anion **14**. the reaction is totally regioselective. The formed triazolyl anion can be protonated giving **15**, carboxylated to afford **16** and can be treated with different azides to afford the linear triazene **17**. The later can be hydrolyzed to give the corresponding triazolamine **18** (**Scheme 5**)[31–33].



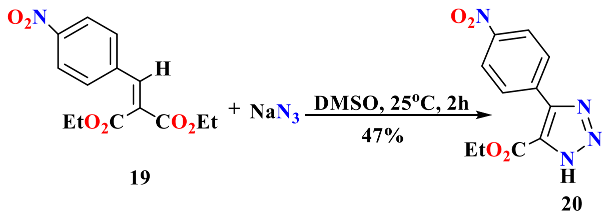
R^1 = Me

R^2 = alkyl, aryl, solfonyl

Scheme 5

1.4. From Activated Alkenes with Azides

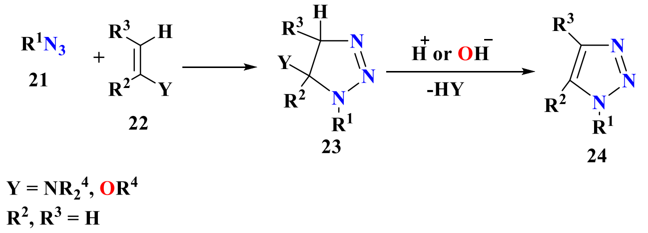
Sodium azides added to alkenes bearing strongly electron-withdrawing groups to afford N-unsubstituted 1,2,3-triazoles (**Scheme 6**)[34–36]. The mechanism of the reaction involved conjugated addition of the azide ion to the double bond of the alkene, followed by cyclization of the resulting anion and then aromatization.



Scheme 6

1.5. From Azides with Enamines or Enol Ethers[37–39]

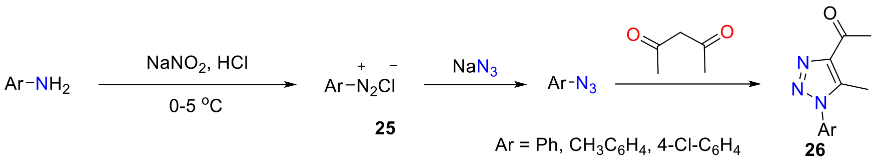
Azides were undergone addition to enamines **22** and to enol ethers under mild reaction conditions at RT giving 4,5-dihydro-1*H*-1,2,3-triazoles **24**. These reactions are totally regioselective (**Scheme 7**).



Scheme 7

1.6. From Active Methylenes with Azides[30,40]

The condensation of active methylenes with azides (Dimroth reaction) in the presence of base as a catalyst is an excellent method for the synthesis of 1*H*-1,2,3-triazole derivatives. It was first reported by Dimroth in 1902. The mechanism of the reaction can be described as a nucleophilic attack on the terminal nitrogen of the azide by the carbanion, followed by cyclizatoin then aromatization. Condensaton of aryl azide with pentane-2,4-dione in the presence of methanol and sodium methoxide gave the corresponding 1,2,3-triazole derivatives **26** (**Scheme 8**).



Scheme 8

2. Reaction of 1,2,3-Triazoles

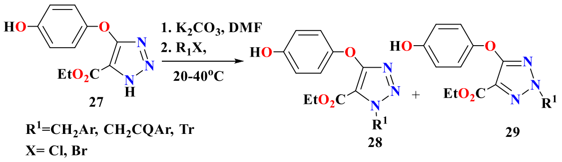
2.1. Alkylation [41–43]

1,2,3-Triazole derivatives can be C- and N-alkylated. N-alkylation is performed by one of the following methods: (**I**) By the reaction with methyl fluoro-sulfonate, diazomethane, alkyl halides, methyl tosylate or dimethyl sulfate (**II**) via Mannich reaction. base is essential in the alkylatoin with alkyl halides; in general, sodium hydroxide, sodium alkoxide and sodium hydride are used.

A mixture of N-alkyl derivatives formed by the alkylation of N-unsubstituted 1,2,3-triazoles. 1,2,3-Triazoles themselves and the symmetrical 4,5-disubstituted triazoles afford a mixture of 1- and 2-alkyl derivatives while unsymmetrical 4,5-disubstituted triazoles afforded all the three possible monoalkyl isomers. When thallium or silver salts of the 1,2,3-triazole derivatives are reacted with iodoalkanes some selectivity observed.

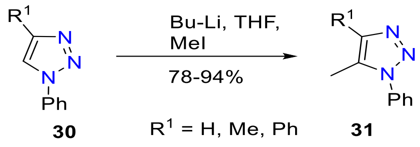
Alkylation of "ethyl 4-(4-hydroxyphenoxy)- 1,2,3-triazol-5-carboxylate" **27** under basic conditions affords N_2 and N_3 alkylation isomers (**Scheme 9**).

On the other hand, alkylation of ethyl 4-(4-hydroxyphenoxy)- 1,2,3-triazol-5-carboxylate **27** with benzyl chloride yields 1:1 mixture of the two derivatives, with 4-bromophenacyl bromide preferred substitution at N_2. While alkylation with trityl chloride ($(C_6H_5)_3CCl$) shows a significant steric preference for the less hindered N_2 position. So, isomer **29** was formed.



Scheme 9

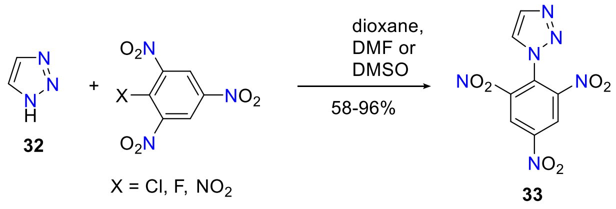
C-Alkylation of 1,2,3-triazoles is achieved by lithiation then addition of an alkyl halide. An authentic sample; the reaction of 1-phenyl-1,2,3-triazole **30** with butyllithium with the addition of iodomethane affords 5-methyl-1-phenyl-1*H*-1,2,3-triazole **31** (**Scheme 10**).



Scheme 10

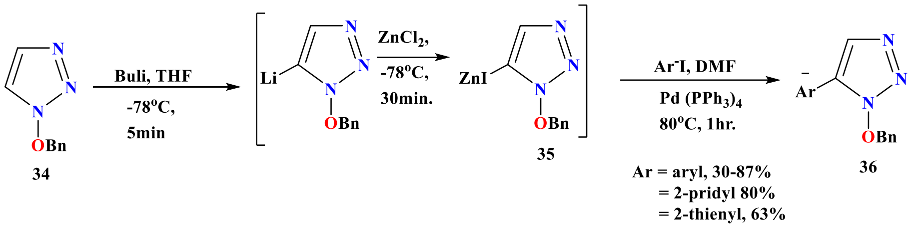
2.2. Arylation [44,45]

1,2,3-Triazoles can be N-arylated using activated aryl halides. Treatment of 1,2,3-triazoles with 1-fluoro-4-nitrobenzene or 1-fluoro-2-nitrobenzene affords mixtures of the 1- and 2-nitrophenyl-1,2,3-triazoles. While, with 4-dinitrobenzene, 1-fluoro-2, and 2-chloro-1,3,5-trinitrobenzene the 1-substituted derivatives are only formed (**Scheme 11**).



Scheme 11

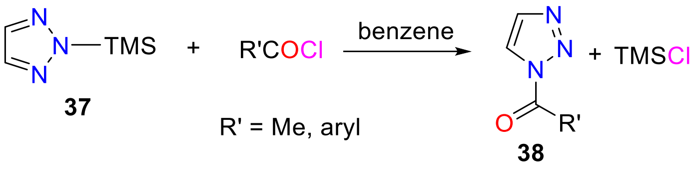
1,2,3-Triazoles are also C-arylated. The palladium-catalyzed reaction of the 1,2,3-triazol-5-ylzinc iodide types **34** with the appropriate of aryl and hetaryl iodide afforded the 5-aryl-1-or 5-hetaryl-1,2,3-triazoles **36** (**Scheme 12**).



Scheme 12

2.3. Acylation[41,46–48]

1,2,3-triazoles can be N-acylated utilizing anhydrides and acyl halides in pyridine or dry benzene as a solvent. The reaction takes place at position 1- but the acyl group may transfer to the position 2- on the presence of base or on heating. Consequently, Acetylation using acetyl chloride affords 1-acetyl isomers which then rearrange to the 2-isomers at temperature above 120°C. While acetylation with acetic anhydride on heating affords 2-acetyl isomers directly. An alternative synthetic method to 1-acetyl-1,2,3-triazole isomers is the treatment of 2-trimethylsilyl isomer for example **37** with acetyl chloride, yielding derivatives such as **38**[48] (**Scheme 13**).

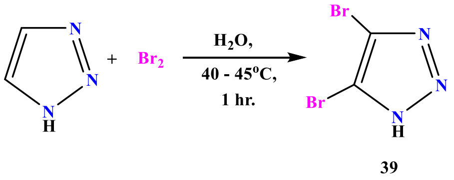


Scheme 13

When 4,5-diphenyl-1,2,3-triazole was submitted to react with benzoyl chloride in pyridine affords the corresponding 1-benzoyl derivative.

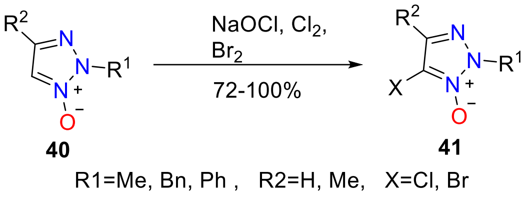
2.4. Halogenation[49–52]

The reaction of 1,2,3-triazole, 4,5-dimethyl-, 4-methyl, 2-methyl, 1-methyl -1,2,3-triazole with bromine, chlorine, hypobromite, hypochlorite and hypoiodite has been reported. 1,2,3-Triazole submitted to react with bromine affording 4,5-dibromo-1,2,3-triazole **39**[52] (**Scheme 14**). The formed intermediate cannot be isolated; it brominated faster than the starting materials. 4,5-Dibromo-1,2,3-triazole is also synthesized in yields 90-95% by bromodecarboxylation of 1,2,3-triazol-4-carboxylic acid[52].



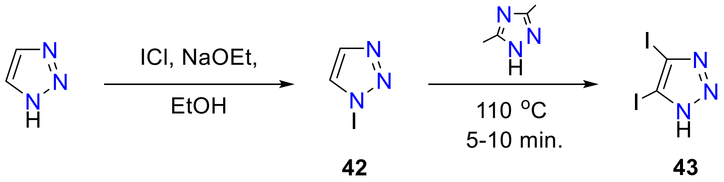
Scheme 14

1-Methyl- and 4-methyl-1,2,3-triazoles were treated with bromine to afford, the 4-bromo-1-methyl and 5-bromo-4-methyl-1,2,3-triazole, respectively. The isomer 2-methyl-1,2,3-triazole less reactive toward halogenations. They react with bromine only in the presence of iron filings as a catalyst and yields 4,5-dibromo-2-methyl-1,2,3-triazole the mono-brominated isomer is not trapped. 2- and 3-substituted-1,2,3-triazol-1-oxides were halogenated selectively in position 5 (**Scheme 15**).



Scheme 15

1,2,3-triazole was submitted to react with iodine monochloride affording 1-iodo-1,2,3-triazole **42**. Melting of a mixture of this compound with 3,5-dimethyl-1,2,4-triazole for 10 mints yields 4,5-diiodo-1,2,3-triazole **43**, when treated with excess amount of sodium hypobromite (**Scheme 16**)[52,53].



Scheme 16

3. Conclusion and Future Prospect

1,2,3- triazoles and their analogies have been reported to be effective against different human diseases. They revealed a potent effect as anticancer agents, antimicrobial agents, anti-inflammatory. The distinguished biomedical and pharmaceutical effect of 1,2,3-triazoles and their derivatives resulting from their effective binding to the to the active sites of DNA gyrase, dihydrofolate reductase, D-alanine-D-alanine ligase, sterol 14-α-demethylase enzyme through hydrogen bonding, hydrophobic interactions, and electrostatic interactions, and etc. consequently, Investigation of novel 1,2,3-triazole based molecules still active area attracted the scientists and researchers from different sectors. The current review discussed the different synthetic methods reported for 1,2,3-triazoles and their derivatives. Additionally, the review discussed the future chemical transformations for production of novel pharmaceutically bioactive 1,2,3-based molecules. Development and investigation of novel 1,2,3-triazoles will be useful for further production of novel, more effective drug like candidates.

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