# Synthetic Trends Followed In The Synthesis of Triazole Derivatives

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ABSTRACT

Triazole ring system has attracted a continuously growing interest of synthetic organic chemists and those dealing with the medicinal compounds due to its versatile potential to interact with biological systems. The triazole compounds possess a wide range of biological activities and are especially focused for antifungal behavior. In this review article, we have summarized the recent developments in the synthetic methodologies of this ring system. 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. The main focus was on the methodologies which deal with the facile and convenient synthesis.

**Keywords:** Triazole ring, Organic chemists, medicinal

## 1.1. Introduction:

Heterocycles form by far the largest of classical divisions of organic chemistry and are of immense importance biologically and industrially. The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic while countless additives and modifiers used in industrial applications ranging from cosmetics, reprography, information storage and plastics are also heterocyclic in nature. Onestriking structural feature inherent to heterocycles, which is exploited to great advantage by the drug industry, lies in their ability to manifest substituents around a core scaffold in defined three dimensionalrepresentations. For more than a century, heterocycles have constituted one of the largest areas of research in organic chemistry. Heterocycles have contributed to the development of society from a biological and industrial point of view as well as to the understanding of life processesto improve the quality of life. Among the approximately 20 million chemical compounds identified by the end of the second millennium, more than two-thirds are fully or partially aromatic and approximately half are heterocyclic. The presence of heterocycles in all kinds of organic compounds of interest in electronics, biology, optics, pharmacology, material sciences and so on is very well known. Between them, sulphur and nitrogen-containing heterocyclic compounds have maintained the interest of researchers through decades of historical development of organic synthesis [1].

However, heterocycles with other heteroatoms such as oxygen, [2] phosphorus[3] and selenium[4] also occurs. Many natural drugs[5-8] suchas papaverine, theobromine, quinine, emetine, theophylline, atropine, procaine, codeine, reserpine and morphine are all heterocycles. Almost all the compounds, known as synthetic drugs such as diazepam, chlorpromazine, isoniazid, metronidazole, azidothymidine barbiturates,antipyrine, captopril and methotrexate are heterocycles. Some dyes (e.g. mauveine), luminophores, (e.g. acridine orange), pesticides (e.g. diazinon) and herbicides (e.g. paraquat) are also heterocyclic in nature. All these natural and synthetic heterocyclic compounds can and do participate in chemical reactions in the human body. Furthermore, all biological processes are chemical in nature. Such fundamental manifestations of life as the provision of energy, transmission of nerve impulses, sight, metabolism and the transfer of hereditary information are all based on chemical reactions involving the participation of many heterocyclic compounds, such as vitamins, enzymes coenzymes, nucleic acids, ATP and serotonin [9].

Although heterocyclic compounds may be inorganic, most contain within the ring structure at least one atom of carbon, and one or more elements such as sulfur, oxygen, or nitrogen [10]. Since non-carbons are usually considered to have replaced carbon atoms, they are called heteroatoms. The structures may consist of either aromatic or non- aromatic rings. Heterocyclic chemistry is the branch of chemistry dealing with the synthesis, properties, and applications of heterocycles. Heterocyclic derivatives, seen as a group, can be divided into two broad areas: aromatic and non-aromatic. In Figure 1.1, five-membered rings are shown in the first row, and the derivative (1) corresponds to the aromatic derivative, furan, while tetrahydrofuran (2), dihydrofuran-2-one (3), and dihydrofuran-2,5-dione (4) are not aromatic, and their reactivity would benot unlike that expected of an ether, an ester, or a carboxylic anhydride, respectively. The second row shows six-membered rings, initially in an aromatic form as pyridine (5), while piperidine (6), piperidin-2-one (7),and 1,2,3,4-tetrahydropyridine (8) are not aromatic; their reactivity wouldnot be very different from that expected of an amine, amide, or enamine, respectively. In general, the reactivity of aromatic heterocycles, which isa combination of that expected from an aromatic system combined with the influence of the heteroatoms involved, is usually more complex, whilethe reactivity of the non-aromatic systems is not too different from the usual non-cyclic derivatives. Thus, most books on heterocyclic chemistry are mainly devoted to the reactivity of aromatic compounds.

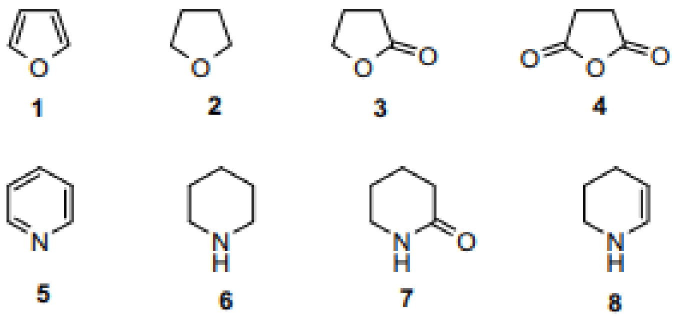


Figure (1.1) Examples of heterocyclic compounds.

### 1.1.1. Triazole:

Triazole, also known as pyrrodiazole, is one of the classes of organic heterocyclic compounds containing a five membered diunsaturated ring structure composed of three nitrogen atoms and two carbon atoms at non-adjacent positions. Two isomers of triazole are [11]:

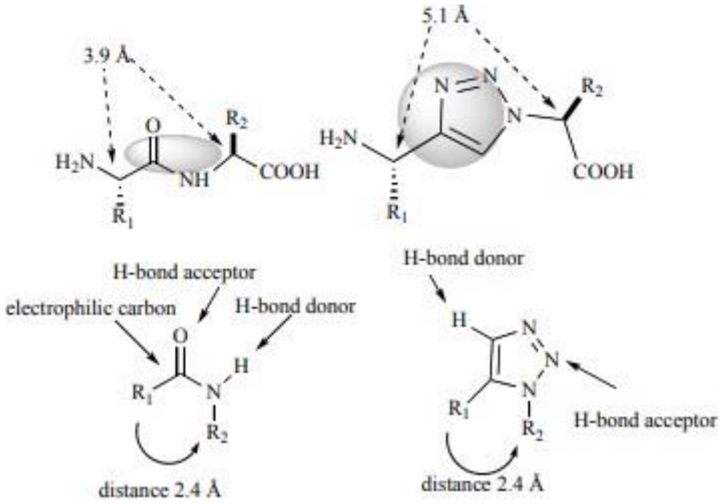
Figure (1.2) Tautomers of 1,2,4-triazoles

Bearing three nitrogen atoms in the ring exist in two isomeric forms namely 1,2,3-triazoles and 1,2,4-triazoles (Figure 1.2). 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 . Over the past decade, scientists across the globe have shown substantial interest in the synthesis of 1,2,3-triazole units . This moiety can be found in a number of pharmaceutical agents as shown in Figure (1.3). Tazobactam, a α-lactamase inhibitor, contains this moiety . Cefatriazine, an orally active semisynthetic cephalosporin antibiotic and rufinamide, an anticonvulsant agent bear 1,2,3-triazole . This moiety finds several applications in the medical field such as antitubercular antibacterial, antifungal ,anticancer, antioxidant , antimalarial , antidiabetic, etc [12].

Figure (1.3) 1,2,3-Triazole bearing drugs

## 1. 1. 2. Pharmacological Significance of Triazole

Due to the interesting physicochemical properties of triazole scaffolds and its stability towards oxidative, reductive and enzymatic hydrolysis, these units are placed in a good position in the pharmaceutical domain. The major role of triazole is found to play in a wide range of medicinal applications such as antifungal, anti-tubercular, anti-bacterial, anti-viral, anti-HIV, anti-tumour, α glycosidase inhibitor, anti-convulsant,anti-allergic, and antiplasmodial agents. These triazoles drugs with anti- fungal properties occupied a good position in clinical applications . The most frequently used anti-fungal bi-triazole-containing clinical drugs are fluconazole, itraconazole, and posaconazole



due to its broad-spectrum antifungal activity, less toxic effect and higher therapeutic indexes. These triazole drugs are fungistatic and comparatively safer than fungicidalpolyenes, amphotericin B. It has been observed that some of the triazole scaffolds of azoles may affect the ergosterol biosynthesis by binding to the iron of the porphyrin ring of the enzyme, cytochrome P450 14α- demethylase (CYP51) . While other triazole-based compounds, such as, ravuconazole, voriconazole and albaconazole are found to be active as antifungal agents, which are either available in the market or are being tested under clinical trials [14].

Fig. (1. 4). Triazole-motif as amide surrogate [14].

### 1.2. Synthetic methodologies for 1,2,3-triazoles

### 1.2.1. 1,3-Dipolar cycloaddition reactions of azides

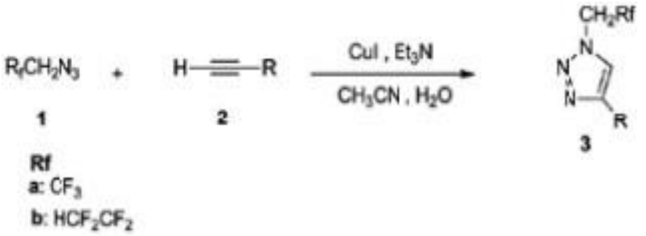
Classic Huisgen reaction which involved thermal 1,3- dipolar cycloaddition of alkynes to azides . This cycloaddition reaction usually affords mixtures of 1,4- and 1,5-disubstituted 1,2,3-triazoles. This method has been widely used for theincorporation of 1,2,3-triazole ring in a broad range of molecules.

The molecule must contain a terminal alkyne, which on treatment with an azide undergo cycloaddition reaction. Recent reports using this methodology are summarized below: In this respect, the classic1,3-dipolar cycloaddition fails as a true click reaction [15].

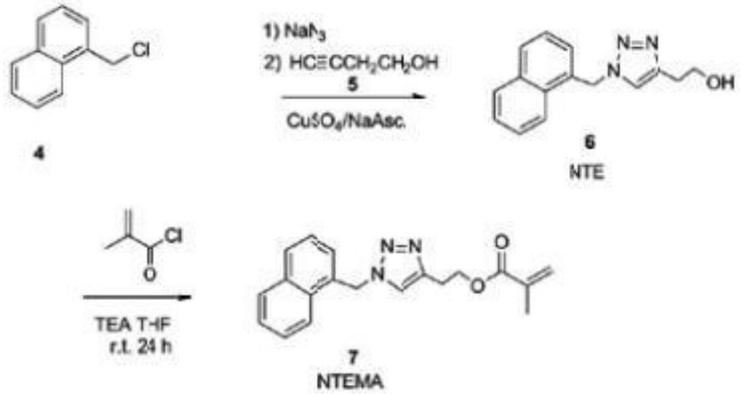
### 1.2.2. 1,3 Dipolar cycloaddition reactions of azides catalyzed by copper salts:

1,4-disubstituted 1,2,3-triazoles with high regioselectivity, are specifically prepared from azides and terminal alkynes under copper (I) catalysis which follows a different mechanism can be conducted under aqueous conditions, even at room temperature. In the mechanism proposed by Sharpless for this reaction, the copper (I) ion is inserted into the terminal alkyne, forming the copper (I) acetylide; this compound reacts with an organic azide and a subsequent rearrangement forms the 1,2,3-triazole product. Because of the existence of copper (I) acetylide , the reaction was regiospecific and only the 1,4-disubstituted 1,2,3-triazolewas formed. A copper catalyzed Huisgen reaction complies fully with thedefinition of click chemistry and is a widespread tool in click chemistry. The regioisomeric 1,5-disubstituted triazoles are available from azides and terminal alkynes by the use of either magnesium acetylides or ruthenium catalysts. There are a huge number of triazole compounds reported by using this method.

A novel disubstituted [1,2,3]-triazoles were synthesiszed by Wu et al. Effectiveness of 1,3-dipolar cycloaddition reaction was enhanced by treating the fluoro-alkylated azides 1 with terminal alkynes 2 (Figure 1.5).Completions of the reaction only lead to the regioselective formation of fluoroalkylated 1,4-disubstituted [1,2,3]-triazoles 3 in the presence ofCu(I) salt as catalyst. [1,2,3] Triazole containing monomer i.e., 2-(1- naphthalen-1-ylmethyl-1H-[1,2,3]triazol-4-yl)-ethyl methacrylate(NTEMA) 7 was prepared by Jin and his coworkers by using clickchemistry and was further subjected to polymerization (Figure 1.6) [15].



Figure(1.5) Synthetic layout for disubstituted [1,2,3]-triazoles by reactionof fluoro-alkylated azides 1 with terminal alkynes tuted [1,2,3]-triazoles by reaction of fluoroalkylated 2.

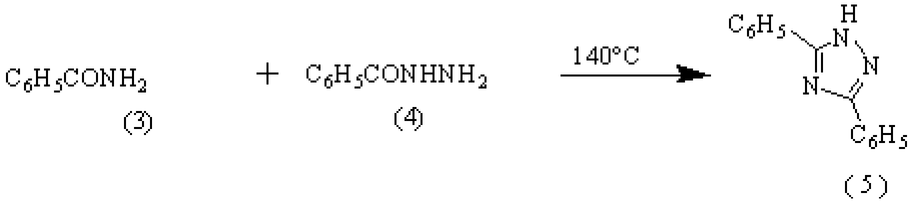


Figure(1.6) Click chemistry synthetic route of 2-(1-naphthalen-1-ylmethyl-1H-[1,2,3]triazol-4-yl)-ethyl methacrylate.

## 1.3. Synthesis of 1,2,4_ Triazol derivatives

### 1.3.1. Pellizzari Reaction

The synthesis of 1,2,4-triazole derivatives by the mixture of amide and acyl hydrazide is generally referred to as the Pellizzari Reaction. It has been reported that heating the mixture of formamide and hydrazine hydrochloride with KOH yield of 1,2,4- triazole. For example benzamide and benzoyl hydrazide gave 3,5- diphenyl-1,2,4-triazole [16].

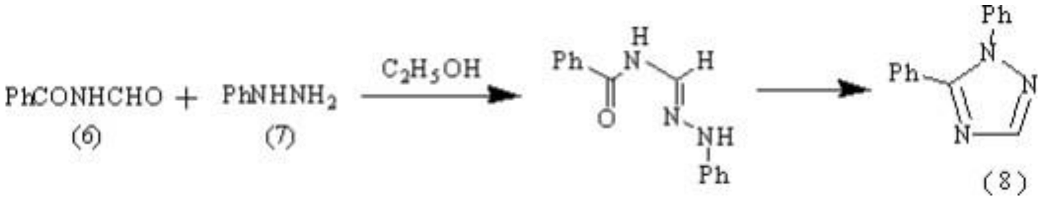


### 1.3.2. Einhorn- Brunner Reaction

The synthesis of 1,2,4-triazoles by condensation between hydrazines or mono substituted hydrazine and diacylamines in the presence of weak acid is known as the Einhorn–Brunner reaction. For example: N-formyl benzamide and phenyl hydrazine gave 1,5- diphenyl1,2,4-triazole [16].

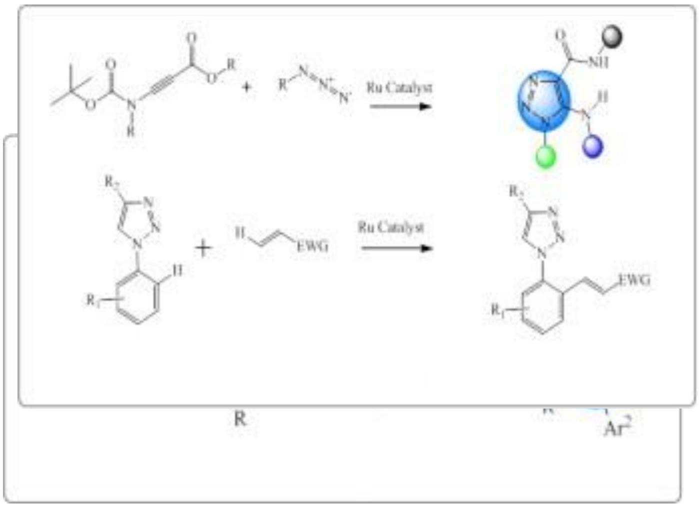
### 1.3.3. Synthesis using metals

**Copper catalyzed 1,3-dipolar cycloaddition:** Copper caltalyzed 1,3-dipolar cycloaddition reaction between an alkyne and azide (CuAAC) is the most commonly employed method for the synthesis of 1,2,3- triazoles [17]. 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 [17]. Zheng and Shi reported a Cu-catalyzed route taking N-tosylhydrazones and azides as the substrates . Chen and co-workers have also demonstrated 1,2,3-triazoles synthesis from N-tosylhydrazones and anilines . An overview of these routes is provided in Figure (1.7).



**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 rutheniumcatalyzed synthesis of 5-amino-1,2,3-triazoles . Ruthenium(II) carboxylate complexes were used for efficient cross-dehydrogenative alkenylations of N-aryl-1,2,3-triazoles [17]. These routes have been shown in Figure (1.8).

Figure(1.7) Copper catalyzed synthesis of 1,2,3-triazole.



Figure(1.8) Reaction routes using ruthenium catalyst.

**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 [17]. Overview of this reaction is given in Figures (1.9) and (1.10).

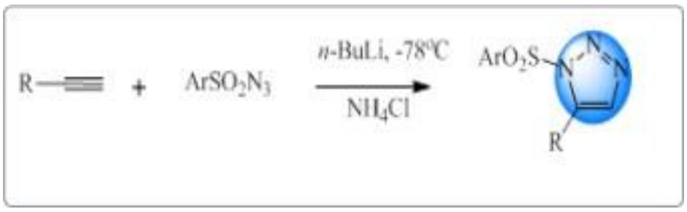


Figure (1.9) Lithium Catalyzed Reaction

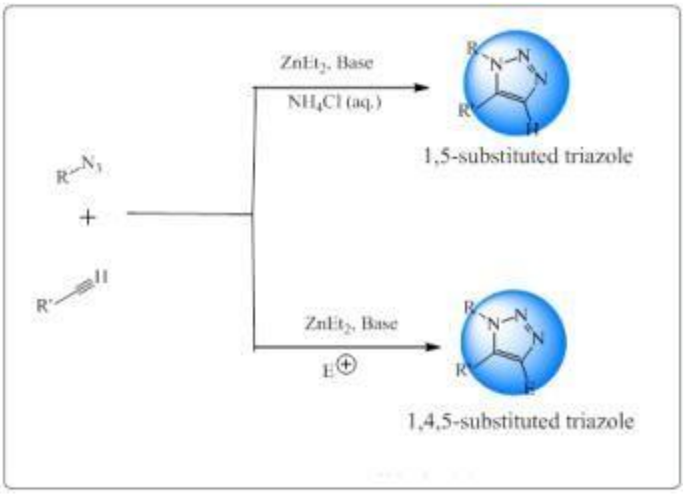


Figure (1.10) Zinc mediated reaction of 1,2,3-triazole.

**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 [17].

### 1.3.4. 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. 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. 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. 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 inthe presence of DBU. Jia et al. carried out 1,3-dipolar cycloaddition of commercially available aldehydes with azides and secondary amines in the absence of metal catalyst [17]. Overviewof all routes is given in Figure (1.11).

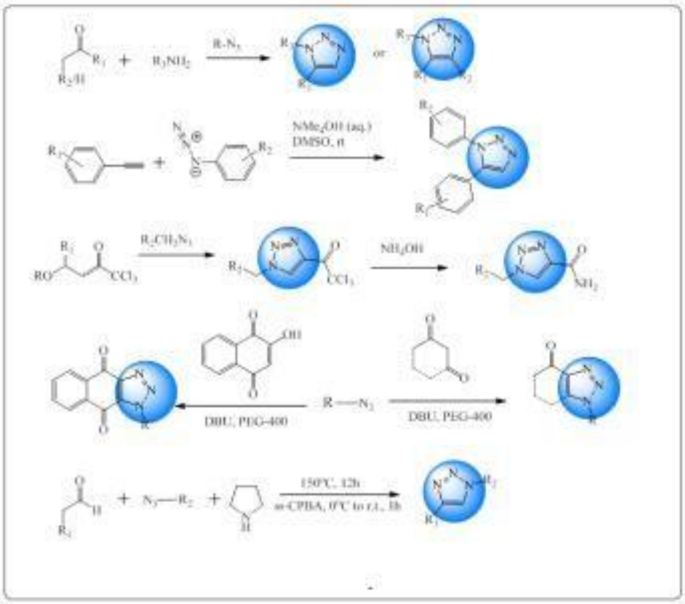


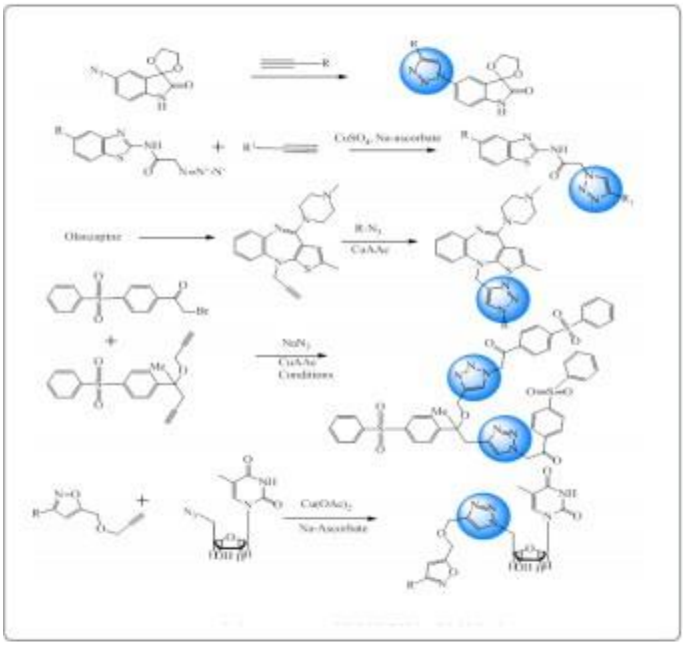
Figure (1.11) Metal-free synthetic routes for synthesis of 1,2,3-triazolederivatives.

### 1.3.5. 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 [18]. 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/H2 O (1:1 v/v) with CuSO4

.5H2 O as the catalyst [17]. 1,2,3-triazoles as PDE4 inhibitors were prepared by CuAAC method under ultrasound irradiation at room temperature. 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 [17]. Zhang and coworkers 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 [17]. Overview of these reactions is given in Figure (1.12).

Figure (1.12) : Ultrasonics assisted reactions.



## Conclusions:

In this study, we have summed up the recent work in the synthesis of triazole ring system. This effort would be useful for common researchers working in the relevant area. Moreover, the research opens a huge scope for exploitation of this ring system as a template for novel useful biologically active compounds. The major focus was to highlight the procedures which were easy to carry out and result in good to excellent yields. It is evident from the above discussion that click chemistry route has been utilized by a vast majority of researchers for the introduction of 1,2,3-triazole ring system. On the other hand, use ofthiosemicarbazide and thiocarbamate intermediates were among the most highlighted methodologies for incorporation of 1,2,4-triazole ring system.In addition, the advancements in the click chemistry synthesis and the methods dealing with environmental friendly procedures were also discussed.

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.

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