Current Developments in the Syntheses of 1,2,4-Triazole Compounds

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Abstract: Heterocyclic 1,2,4-triazole derivatives possess unusually spacious potentiality as medicinal agents, agricultural chemicals, functional materials, ionic liquids, supramolecular catalysts as well as artificial enzymes and receptors for supramolecular recognition and mimetic catalysis, and their various researches and developments have being a quite rapidly developing and active highlight topic with an infinite space. Numerous efforts have been directed toward various types of possible applications of 1,2,4-triazole-based compounds and a lot of important progress has been made, especially their preparations have attracted increasing attention. This review systematically summarized the recent advances in the syntheses of 1,2,4-triazole derivatives, including: (1) Cyclizations to form triazole ring; (2) Transformations of heterocyclic compounds to construct triazole ring; (3) Substitutions on 1,2,4-triazole ring; (4) Structural modifications in side chains of 1,2,4-triazole ring. It was hoped that this review would be helpful for the design and development of highly efficient preparation of 1,2,4-triazole derivatives with various sorts and varieties of extensively potential applications in medicine, agriculture, chemistry, materials, supramolecular sciences and so on.

Keywords: N-Alkylation, cyclization, heterocyclic transformation, hydrazine, hydrazone, N-quaternization, structural modification, 1,2,4-triazole.

1. INTRODUCTION

Triazole compounds have been attracting special interest due to the presence of unusual five-membered tri-nitrogen aromatic heterocyclic structure which may exert diverse weak interactions such as hydrogen bonds, coordination, ion-dipole, cation-π, π-π stacking, hydrophobic effect, van der Waals force and so on [1, 2], and thereby 1,2,4-triazole-based compounds exhibit extensively potential applications in medicinal, agricultural, chemical, supramolecular as well as materials sciences [3,4]. In medicinal chemistry, the unique structure of triazole ring made its derivatives easily bind with a variety of enzymes and receptors in biological system and show broad biological activities like antibacterial, antifungal, antiviral, anticoagulant, anti-inflammatory, anticancer and antioxidant properties etc [5-7]. So far, a large number of triazole-based medicinal drugs have been extensively used in clinic, such as antifungal Fluconazole 1, Voriconazole 2 and Itraconazole 3, anticancer Letrozole 4 and Anastrozole 5 as well as antiviral Ribavirin 6 (Fig. 1) [8, 9]. More importantly, numerous researchers have been devoting to triazole compounds as medicinal agents and hopefully discover novel chemical scaffold compounds with broad spectrum, high bioactivity, low toxicity and excellent pharmacokinetic property. Noticeably, more and more triazole-based compounds as drug candidates are being actively developed [10]. In agriculture, triazoles as agrochemicals, for example, fungicides, plant growth regulators, herbicides and insecticides etc. play an unusually important role in ensuring the harvest of the crops [11-13]. A lot of triazole pesticides such as insecticide Triazophos 7, fungicides Triadimefon 8 and Prothioconazole 9, plant growth regulators Paclobutrazol 10a and Diniconazole 10b, herbicides Sulfentrazone 11 and Fluopaxam 12 (Fig. 2) have been extensively employed for agricultural production. In material sciences, triazoles as new types of functional materials have displayed enormous potentiality in luminescent, magnetic and electron transport materials [3,14-19]. In chemical aspects, as corrosion inhibitors, triazole-derived compounds may easily form π-coordination bonds with various metal ions to inhibit the corrosion of metals [20, 21]; as light stabilizers, triazole derivatives with low volatility and high thermostability have been widely applied in paints, food packages as well as sunscreen agents [11]. As a new type of ionic liquids (ILs), triazoles have exhibited conspicuous advantages with nonvolatile, wide applicable temperatures and environmentally friendly properties [22,23]. In supramolecular chemistry, the specific 1,2,4-triazole ring as good building block has been frequently employed to construct various artificial cation, anion and molecular receptors [3,24], enzyme models and supramolecular catalysts [25, 26] as well as nanometer materials [3,27], especially in supramolecular recognition, assembly [28, 29] and in the development of supramolecular drugs [30-32]. All the above mentions have strongly shown an infinite space for the various applications of triazole compounds. In fact, numerous works have been focusing on various types of possible applications of 1,2,4-triazole-based derivatives, and a large number of excellent achievements have been acquired. The related researches have become a quite rapidly developing and increasingly attracting highlight topic [33-35].

The extensive potential applications of 1,2,4-triazole-based compounds have attracted increasingly overwhelming effort to develop their highly efficient syntheses [2,36-38]. Numerous works have been directed toward their syntheses with cheap and easy preparations, and a great deal of progress has been acquired [39, 40]. Throughout current researches, the synthetic methods of triazole compounds could be principally divided into two pathways: the formation of triazole ring and the functionalization of triazoles. The constructive routes of triazole ring include the cyclizations or cycloadditions from non-cyclic compounds and transformations of...
other heterocycles. In particular, cyclization approaches, due to good yields, mild reaction conditions and easy operations as well as commercial availability for reactant materials with cheapness and convenience, were the most predominant methods to produce 1,2,4-triazoles especially various substituted triazole derivatives. The structural modifications of triazole compounds were also extensively adopted to prepare new triazole derivatives. Noticeably, the N-alkylation modifications of triazole ring have been being prevalent synthetic strategy to develop bioactive 1,2,4-triazole containing compounds especially antimicrobial drugs with broad active spectrum, high efficiency and low toxicity. A large number of works have also focused on the structural reconstitutions in the side chains of triazole ring. Furthermore, some synthetic techniques like combinatorial chemistry, solid-phase synthesis, and microwave-assisted synthetic technology as well as other methods such as one-pot preparation, highly selective reactions and asymmetric synthesis and phase transfer catalysis etc. have been extensively developed and employed for the preparation of various triazoles. Previously, a few works had partially introduced the synthetic methods for some types of 1,2,4-triazoles [2,36,38,41]. However, so far no comprehensive review on current synthetic methods of various 1,2,4-triazole compounds has been observed. This review should be of great interest to the readers as it for the first time systematically summarized the current developments in the syntheses of 1,2,4-triazoles, including (1) Cyclizations to form triazole ring; (2) Transformations of heterocyclic compounds to construct triazole ring; (3) Substitutions on 1,2,4-triazole ring and (4) Structural modifications in side chains of 1,2,4-triazole ring. The comparable discussion of various types of synthetic methods to access triazoles was done. The perspectives of the foreseeable future in the new trend of synthetic developments for the preparation of 1,2,4-triazoles were also presented. It is hoped that this review will be helpful to serve as a stimulant for new thoughts in the quest for rational designs of highly efficient preparation for various sorts and varieties of 1,2,4-
triazole derivatives with diverse potential applications in chemical, medicinal, agricultural, material sciences and so on.

2. CYCLIZATIONS TO FORM TRIAZOLE RING

Cyclization is one of the most important synthetic methods in the preparation of 1,2,4-triazole derivatives with adjustable substituents like mono-, bis- and tri-substituted ones. An increasing number of researches have directed toward the cyclization reactions to prepare 1,2,4-triazole ring with desirable various structural substituents. Among these cyclizations to prepare 1,2,4-triazole derivatives, hydrazide and its derivatives are the most common starting materials to form the C=N or C–N bonds and have been extensively investigated. Especially, the dipolar cycloaddition as a predominantly synthetic method is widely employed to build 1,2,4-triazole scaffold with special structures.

The simple non-substituted 1H-1,2,4-triazole is commercially available with very cheapness. So far its preparative methods are mainly involved in four types of synthetic methods [42, 43]: (1) Cyclization of formylhydrazide with formamide. This preparative method provides quite low yield. (2) Cyclization of formic acid with hydrazine hydrate and formamide. This type of synthetic procedure takes long reaction time and is not applicable for industry production. (3) Cyclization of formic acid with hydrazine hydrate under ammonia gas. The first step of this method is two phase reaction with harsh conditions and long reaction time. (4) Cyclization of formamide with hydrazine hydrate in a mole ratio of 3:1. This approach as the maturely synthetic method with simple operation and high yield has been popularly employed for the preparation of 1H-1,2,4-triazole in industry. In spite of this, some effort has been still directed toward the further synthetic improvement and here the detailed advance will not be described. The present works almost focus on the synthetic developments of 1,2,4-triazole derivatives.

The substituted 1,2,4-triazole compounds, covering specific substituents or substitution patterns, have been attracting special interest due to their extensive applications in many fields. Currently, there are thousands of scientific papers describing the syntheses of this versatile group of triazoles. The reported synthetic methods of substituted triazoles could be summarized into the following categories according to the different precursors of cyclization reactions to form 1,2,4-triazole ring: (1) Hydrazones; (2) Hydrazides; (3) Hydrazines; (4) Guanidines and so on.

2.1. Cyclizations of Hydrazones

Hydrazones as important synthons have been extensively adopted to construct 1,2,4-triazole ring. The cyclization of hydrazones with nitrile compounds is an earlier synthetic method for the formation of 1,2,4-triazole backbone. Up to now, a large amount of work has been devoted to hydrazones and their derivatives as precursors for the preparation of triazole derivatives [36-38]. On the basis of the different substituents on hydrazone skeleton, the starting reactants for the syntheses of 1,2,4-triazole derivatives may be recapitulated in the following types: amidrazones, acyl hydrazones and other hydrazone derivatives.

2.1.1. Amidrazones

Amidrazones, the conjuncted products of imine and hydrazines, are a class of important reactants for the synthesis of various types of nitrogen-containing compounds with broad bioactive spectrum, interesting luminescent and magnetic properties [44,45]. Their cyclization with carbonyl compounds is one of the most important pathways to access 1,2,4-triazole derivatives [46-48].

It is well known that the preparation of aryl triazoles is a huge challenge to synthetic chemists, and much effort has been contributed to the synthetic developments of this type of triazoles [49]. Currently, the prevalent preparative strategy is the classical synthetic method of transition-metal-catalyzed carbon-carbon cross-coupling. However, the costliness and instability of organometallic reactants largely limit their application. Great hope has therefore been invested in multicomponent heterocyclization which is able to readily access aryl triazoles under mild reaction conditions without the preparation of any organometallic intermediates. A practical example was the multicomponent reaction of primary hydrazones 13, substituted iodobenzene 14 and carbon monoxide under the catalysis of palladium diacetate that could facilely produce the substituted 1,2,4-triazole 15 with acceptable yields ranging from 56% to 79% (Scheme 1) [49].

The cyclization of this substituted amidrazones to afford sulfur triazoles is a special interesting topic because this type of thio triazole compounds generally exhibits broad bioactive spectrum. The reaction of sulfur substituted hydrazine 16 with a series of aliphatic and aromatic primary amines in boiling glacial acetic acid was expected to produce N-substituted amides of 3-(3-ethylthio-1,2,4-triazol-5-yl)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid, but it failed. Interestingly, during cyclization reaction nucleophilic ring opening and decomposed. X-ray analysis elucidated that an unexpected product, the N-substituted amides of 3-(3-ethylthio-1,2,4-triazol-5-yl)propenoic acid 17, was obtained in good yields. The electron withdrawing substituents on benzene ring seemed to be in favor for this conversion and resulted in high yields for 17a (R = 2-Cl) and 17b (R = 4-Br) with 81% and 78% respectively, while compound 17c with electron donating 3-CH3 group gave relatively low yield (67%) (Scheme 2). Additional researches showed that the introduction of sulfur atom into triazole compounds could evidently improve lipophilicity and regulate electron density of triazole ring, thus enhancing anticancer activities [50].

With the advent of ever more sophisticated computational methods for the modeling of molecular skeletons and properties, it is unsurprising that this has opened a new direction in the exploitation of novel drug scaffolds and could also predict the possibility for the synthesis of completely new bioactive organic molecules. Theoretical calculations suggested that cyclization of phenyl hydrazine 18 with commercially available cis-1,2-cyclohexanedicarboxylic anhydride could generate antimicrobial 3,4,5-trisubstituted triazole 19 which practically exhibited antimicrobial activity against the tested fungi. The experimental results indicated that the temperature largely influenced the formation of target compound 19, and the room temperature was favorable for the formation of the desired product, while the refluxing condition resulted in the cyclic imide with 78% yield under the molar ratio of 1:1 for the two reactants (Scheme 3) [51].

Recently, much attention has been directed towards this type of reaction as shown in (Scheme 3) with an aim to extend its applicable scope and functional group tolerance. Substituted hydrazide 20, a pyridine analog of compound 18, could react with itaconic anhydride 21 in anhydrous diethyl ether at room temperature for 7 days to produce trisubstituted triazole 22a in a quite low yield of 15%, and while the mixture was treated by aqueous sodium hydroxide (2%) under reflux condition to give its isomer 22b in 75% yield. In order to further recognize this reaction, more efforts were done and found that compound 22a could be transformed into the more stable isomer 22b when treated by 2% NaOH solution at room temperature for 12 h or in dimethylformamide (DMF) at 150 °C for 4 h (Scheme 4) [52].
The cyclic substituted hydrazone 23 was obtained through Beckmann rearrangement of oxime in the presence of polyphosphoric acid (PPA) and subsequent treatment with phosphorus pentasulfide and hydrazine hydrate, its cycloaddition with formic acid could favorably produce anticonvulsant oxazepine triazole 24 in yields of 71-83%. The length of alkyl chain had no large effect on the yields of compound 24, but exerted direct impact on anticonvulsant activity (Scheme 5) [53]. The easy preparation of oxazepine triazole derivatives provides a large possibility for their further exploitation of new oxazepine triazoles with low neurotoxicity and potent anticonvulsant activity.

Morpholine containing hydrazone 25, a six-membered analog of compound 23, was a good precursor for the preparation of triazolium compounds. It could easily react with trimethyl orthoformalte to produce triazolium 26 in almost quantitative yield, and the latter as the precursor of N-heterocyclic carbenes (NHC) was able to form metal complexes with metal ions [54]. This type of triazolium metal complexes was generally resistant to decomposition and could be used as catalysts without additional ligands (Scheme 6) [55-57]. Some other triazolium compounds such as pyridine-based triazoliums [58] could also be successfully prepared in high yields by this method and all the triazolium compounds were found

Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.

Scheme 5.
to exhibit much potentiality for further utilization in coordination and organometallic chemistry.

Benzene bridged bis-morpholine hydrazone 27, a condensed product resulting from \( m \)-phenylenedihydrazine and the corresponding morpholin-3-one, could successfully undergo cyclization with triethyl orthoformate to form triazole compound 28 in overall yields of 51-64%. Bis-triazolium 28 was a good catalyst that could efficiently catalyze the asymmetric intermolecular benzoin condensation in the presence of \( t \)-BuOK (Scheme 7) [59].

Solvent-free conditions (SFC) have been attracting special interest in synthetic chemistry because of no risk to use large amounts of volatile organic solvents and no need to recover, purify and reutilize the solvents [60]. In SFC, the substitution of ethoxy group in pyrazole 29 by aromatic amines under conventional heating (150 °C, 3 h) readily generated intermediate pyrazole hydrazone 30 and subsequently proceeded intramolecular cyclization to produce pyrazolyl 1,2,4-triazole 31 which could be easily converted by the use of amino group on pyrazole ring into other 1,2,4-triazole derivatives in good yields (Scheme 8) [61].

Silver salts as catalysts are able to promote the cyclization of hydrazones to access 1,2,4-triazole derivatives. Under the catalysis of silver carbonate, aryl amidrazone 32 easily proceeded an intramolecular cyclization in refluxing acetonitrile to successfully afford the desired 1,3,5-trisubstituted 1,2,4-triazole 33 as potential cytochrome P (CYP) enzyme inhibitor (Scheme 9) [62]. This type of preparative method has been usually employed for the formation of triazole ring with low reaction temperature and short reaction time.

Tertiary amino substituted amidrazones are one important type of building blocks for the synthesis of trisubstituted 1,2,4-triazole derivatives which can form coordination polymers by different \( \pi \)-\( \pi \) stacking interactions, especially off-set-face to face arrangements.
Bis-tertiary amino amidrazone 34 with substituted phenylamine in the presence of \( p \)-toluene sulfonic acid (\( p \)-TosOH) underwent intramolecular cyclization to afford 3,4,5-trisubstituted triazole 35. The formed yields were remarkably affected by the substituents on benzene ring (Scheme 10). The presence of bis-carboxyl group resulted in quite low yield of compound 35c (45%), while mono-carboxyl substitution gave high yields up to 70-81% (Table 1). Generally, it was considered that the driving force in this reaction was the release of dimethyl amine as well as the stability of aromatic heterocycle [63].

Thiocarbonyl diazoles as one of the highly reactive molecules are also used for the preparation of triazolones which are difficult to be prepared under common conditions. Treatment of amidrazone 36 with 1,1-thiocarbonyldiimidazole 37 as the donor of the remaining carbon atom in tetrahydrofuran (THF) gave the corresponding 1,2,4-triazol-5-thione 38 in yields of 47-55%, while mono-carboxyl substitution gave high yields up to 70-81% (Table 1). Generally, it was considered that the driving force in this reaction was the release of dimethyl amine as well as the stability of aromatic heterocycle [63].

The aromatic heterocycles with the emission color tunability have recently received a great deal of interest in a variety of photonic applications. In particular, triazole derivatives have been intensely studied as dopants in light-emitting electrochemical cells. Luminescent triazole 40 was prepared by the cyclization of pyridine amidrazone 39 with a series of substituted benzoyl chloride in basic media, and easily isolated by recrystallization without further purification. (Table 2) manifested that substituents on benzene ring exhibited large effect on the formation of triazoles, especially the 4-CH\(_3\) substituent was specially favorable for this cyclization with almost quantitative yield up to 97%. Surprisingly, the presence of 4-OCH\(_3\) group gave low yield of 58%, and further researches to elucidate the influential factors on this reaction were necessary (Scheme 12) [65].

The combination of different pharmacophores into one molecule is a prevalent strategy to design and develop new bioactive compounds. Many works have been contributed to this field to explore the bis-functional drug molecules with the aim to discover highly active drugs. Antitumor benzimidazolyl 1,2,4-triazole 42, a medicinal hybrid of nitrbenzimidazole and triazole, was efficiently prepared in 80% yield by the cyclization of benzimidazole amidrazone 41 with trimethyl orthoformate. The bioactive assay showed

**Scheme 10.**

**Table 1. Effects of Substituents on the Formation of Compounds 35a-e**

<table>
<thead>
<tr>
<th>Compound 35</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
<th>e</th>
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<tbody>
<tr>
<td>R(^1)</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>CH(_3)</td>
<td>CH(_3)</td>
</tr>
<tr>
<td>R(^2)</td>
<td>4-COOH</td>
<td>3-COOH</td>
<td>3,5-(COOH)(_2)</td>
<td>4-COOH</td>
<td>3-COOH</td>
</tr>
<tr>
<td>Yield (%)</td>
<td>70</td>
<td>65</td>
<td>45</td>
<td>77</td>
<td>81</td>
</tr>
</tbody>
</table>

**Scheme 11.**

**Table 2. Effects of Substituents on the Formation of Compounds 40a-g**

<table>
<thead>
<tr>
<th>Compound 40</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
<th>e</th>
<th>f</th>
<th>g</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>H</td>
<td>4-CH(_3)</td>
<td>4-OCH(_3)</td>
<td>4-F</td>
<td>2,6-(F)(_2)</td>
<td>3,5-(F)(_2)</td>
<td>2,3,4,5,6-(F)(_5)</td>
</tr>
<tr>
<td>Yield (%)</td>
<td>63</td>
<td>97</td>
<td>58</td>
<td>72</td>
<td>45</td>
<td>68</td>
<td>60</td>
</tr>
</tbody>
</table>
significant anticancer efficacy and its cytotoxic mechanism involved with reductive alkylation of DNA accompanied by the cleavaging of G and A bases (Scheme 13) [66]. This type of cyclization provides a convenient method for the preparation of novel triazole derivatives with multiple target sites.

Intramolecular cyclization of amidrazone is another alternative strategy to construct triazole compounds. Formyl amidrazone 43, which was obtained by the reaction of ethyl ethoxycarbonyl acetimide with formyl hydrazine, underwent intramolecular cyclization in vacuo at 29 mm Hg to afford triazole 44 in 78% yield, and the prepared ethyl 3-triazolyl acetate could be further treated by ammonia and then dehydrated by P2O5/dry sand/absolute pyridine to generate triazolyl acetonitrile which was an important intermediate of potent inhibitors for vascular endothelial growth factor receptor II (VEGFR-2) (Scheme 14) [67].

Aryl substituted amidrazone 45 could also generate intramolecular cyclization under high temperature to produce bis-aryl triazole 46 (Scheme 15) [68]. This reaction is of great use in preparation of pyridine-triazole-benzene based xanthine oxidoreductase (XO) inhibitors with non-purine structures using acyl amidrazones as intermediates to introduce a heterocyclic moiety for reinforcement activity. However, no yields were given in this literature.

2.1.2. Acyl Hydrazones

Acyl hydrazones also are important starting reactants to construct the backbone of 1,2,4-triazole ring and have been paid large attention due to the easy operations and highly active reactivities [69-71].

Microwave-assisted synthetic technology has been frequently employed in organic synthesis with shorter reaction time, higher yields and more environmentally friendly properties in comparison with traditional methods [72]. Intramolecular cyclization of compound 47 was achieved in water by microwave irradiation without any bases or catalysts to readily produce amino 1,2,4-triazole 48 in excellent yields. Experiments showed that this reaction could be highly affected by the solvents. Water was found to be the best green solvent to promote this reaction, while ethanol was unfavorable for this transformation (Scheme 16) [73].

Intramolecular cyclization of guanidine containing acyl hydrazone 49, which was prepared by the reaction of benzohydrazide with cyano guanidine in the presence of hydrochloric acid, afforded guanidino 1,2,4-triazole 50 in 68% yield and further transformed products 1,2,4-triazolo[1,5-a][1,3,5]triazines may be used as potent inhibitors of A1 and A2A adenosine receptors (Scheme 17) [74]. By the same synthetic procedure, indolyl-4H-1,2,4-triazoles as the center ligands of Growth Hormone Secretagogue Receptor 1a (GHS-R1a) with effective anti-obesity activity could also be efficiently prepared in good yields ranging from 73% to 79% [75]. This synthetic approach provides a practical and useful procedure with easy operation and mild condition for the construction of guanidino substituted triazole derivatives.
Phthalocyanines are a family of aromatic macrocycles with delocalized 18-π electron system which are well known as photodynamic reagents for cancer therapy, laser dyes, new red-sensitive photocopying applications, optical computer read/write discs and so on. Triazole ring is incorporated into phthalocyanine molecules due to the strong ability of triazole derivatives to form metal complexes that extend magnetochemical application and other potential uses as optical sensors or molecular memory devices. Amino triazole 52 with two substituted benzenes was an important precursor for the preparation of triazole phthalocyanines and was easily synthesized in good yield (85%) via intermolecular cyclization of hydrazine hydrate in n-propanol with the acyl hydrazone 51 which was obtained by the condensation of p-chlorobenzohydrazide with ethyl imido-γ-methylbenzoate. Further modification of compound 52 by 2-fluoro-4-chlorobenzyl and 3,4-dicyano phenyl groups and subsequent cyclization afforded triazole derived phthalocyanine which could coordinate with metal ions to form magnetochemical supramolecular complexes (Scheme 18) [76]. This synthetic procedure presents a practical route for the preparation of triazole derived phthalocyanines with multipurpose potentiality.

Ferrocene containing heterocycles also possess various potential applications as medicinal agents, materials, catalysts and so on, especially triazole ones, due to their strong bioactivity and broad bioactive spectrum, have been attracting considerable attention. 1,2,4-Triazole-based bis-ferrocene 54 was prepared by the intramolecular cyclization of 1,5-bis(ferrocenylmethylene)thiocarbonohydrazide 53 under facile methyl iodide and dimethyl acetylenedicarboxylate (DMAD) mediated condition (Scheme 19) [77]. This pathway is an easy synthetic route to prepare 1,2,4-triazole-based diferrocenyl heterocycles.

Ester substituted hydrazones can also be served for the preparation of triazole tautomeric forms triazolones with desirable properties. Imidazole derivatives possess diverse potential application in pharmacology, chemistry and materials sciences [78-81]. Recently, the conjunction of triazole ring with imidazoles has also become the subject of debate. Experiments showed that the reaction of com-

Scheme 17.

Scheme 18.
Compound 55 with N-(3-aminopropyl)imidazole could not proceed smoothly under traditional conditions, but it was able to go rapidly without solvent in sealed tube to give compound 56 which could be used for the precursor of ionic liquids. The X-ray crystallography showed that the three ring system was on one plane in compounds 56a and 56b, while the ring system in 56c was in parallel (Scheme 20) [82]. It seemed no obvious substituent effect, either the electron withdrawing NO2 group or the electron donating OCH3 substituent in phenyl ring made this reaction occur smoothly.

Continuous researches demonstrated that ethoxycarbonyl hydrazine 57 was also able to smoothly perform cyclization with 4-aminoantipyrine to generate the antibacterial pyrazolyl 1,2,4-triazole 58 (78%) which as a hybrid of antipyrine and triazole pharmacophore was expected to display excellent pharmacological profiles with different mechanisms of action, slow metabolic rate, high oral bioavailability and less side effects (Scheme 21) [83].

2.1.3. Other Hydrazones

Literature has reported that 1,3-dipolar cycloaddition as one type of pericyclic reactions relating to six /g1 electrons could perform a versatile and efficient one-pot reaction to access five-membered heterocycles [84-89] particularly triazole derivatives starting from available oximes, hydrazones and hydrazonyl halides [90-92]. The 1,3-dipolar cycloaddition of phenyl substituted hydrazonyl chloride 59 with oxime 60 in the presence of excess triethylamine could generate triazole derivative 61 with broad antimicrobial spectrum (Scheme 22). As shown in (Table 3), the type of R 2 group had great effects on this reaction, the electron donating alkyl oximes 60a-b and 60d-e as well as cycloalkyl compound 60g gave high yields up to more than 87%, while the aromatic and aza-heterocyclic substituents seemed to be unfavorable for this cycloaddition, specially the large 2-naphthyl group made the yield low to 28%. However, the R1 group, which is far away from the reactive center, showed weak effects on the formation of target compound 61 [93, 94].

The phenyl substituted hydrazone 62 could also be readily transformed by amidine into trisubstituted triazole 63 in 63-78% yields through the nucleophilic addition of the imino group in amidine then cyclization at the imine carbon, or by cycloaddition onto C=N of the amidine moiety. Similarly, compound 62 could also smoothly cyclize with oxime to produce triazole compound 63. Researches showed that the substituents on benzenes exhibited little effect on the yields of target compounds (Scheme 23) [95].

The cycloaddition of strongly dipolar 2-arylsulfanylpyridinium N-arylhydrazide 64 with isothiocyanates could form fused thiopyrazolium salt 65 in very good yields (Scheme 24). This transformation may be elucidated as a regular 1,3-dipolar cycloaddition followed by a spontaneous elimination of aryl group [96].

2.2. Cyclizations of Hydrazides

As is well known, several hydrazides are commercially available, and the noncommercial ones could be successfully prepared
derivatives have caused much interest and a lot of works have been directed towards their developments [97-101]. Cyclization of formylhydrazide with 2,3-dihydro-1H-indene thioamide 66, a product of amide with Lawesson’s reagent in toluene, successfully provided triazole intermediate 67 in yield of 22% under the catalysis of mercury acetate (Scheme 25). In comparison with the relatively low yield of this compound, the final target triazole compound as the potent sodium glucose co-transporter 2 (SGLT2) inhibitor unexpectedly exhibited a highly antidiabetic activity. Undoubtedly, further work is necessary to improve the yield of compound 67 [102].

Under the catalysis of acetic acid, hydrazide 68 proceeded cyclization with 4-aminophenol and dimethoxy-N,N-dimethylmethanamine to give phenol containing triazole 69 in excellent yield by one-pot procedure of the three component which has a wide range of applicability with adjustable substituted primary amines, hydrazides and dimethyl acetal as starting materials (Scheme 26) [103]. The maximal electroshock (MES) test showed that this type of synthetic compounds exhibited strong potency at a dose of 30 mg/kg against MES induced seizure in mice and also possessed remarkable lower neurotoxicity [104]. By the similar procedure, triazole fragment was coupled with 2-substituted benzoxazole to give molecules with broad bioactive spectrum [105] and other 4-(hydroxyphenyl)-1,2,4-triazole derivatives were also able to be prepared efficiently [106].

The N-ethylmorpholine substituted hydrazide 70 was treated in trifluoroacetic acid (TFA) by S-methyl isothiourea 71, which was prepared by the conversion of thioureas and secondary amine, to successfully afford the desired antimicrobial 3-N,N-dialkylamino-1,2,4-triazole 72 in 68% yield (Scheme 27) [107]. This synthetic method has been common strategy for the preparation of 1,2,4-triazole bioactive molecules involved the condensation of hydrazides with S-methyl isothiourea because of the relatively mild condition, acceptable yields and good functional group tolerances including various heterocyclic derivatives like morpholine.

The cyclization of substituted hydrazide 73 with azetidine thioamide 74, a tautomeric form of S-methyl isothiourea, in the presence of trifluoroacetic acid produced compound 75 in low yield of 35% (Scheme 28) [108]. Further optimization of the reaction conditions to improve the yields of this transformation is necessary for potential clinical application of compound 75 as a potent oxytocin antagonist.

Computer aided design for organic molecules has attracted great interest and promoted the progress of synthetic chemistry [109]. The theoretical calculation predicted that the reaction of dissubstituted hydrazide 76 with compound 77 could smoothly occur, the experimental result showed that triazole 78 was successfully obtained in the presence of potassium carbonate as anticipated, and could be further transformed in THF at room temperature into azabicyclo[3.1.0]hexyl triazole derivative as potent antagonist of dopamine D3 receptor (Scheme 29) [110].

The ester type of methoxyl substituted hydrazide 79 could also readily proceed cyclization with 4-nitroaniline and trimethyl ortho-

Table 3. Effects of Substituents on the Formation of Compounds 61a-g

<table>
<thead>
<tr>
<th>Compound 61</th>
<th>a</th>
<th>b</th>
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<th>f</th>
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<tbody>
<tr>
<td>R¹</td>
<td>4-F</td>
<td>4-F</td>
<td>4-F</td>
<td>4-CF₃</td>
<td>3-CF₃</td>
<td>4-CF₃</td>
<td>4-CF₃</td>
</tr>
<tr>
<td>R²</td>
<td>CH₃</td>
<td>i-Pr</td>
<td>2-naphthyl</td>
<td>CH₃</td>
<td>CH₃</td>
<td>2-pyryrol</td>
<td>cyclopentyl</td>
</tr>
<tr>
<td>Yield (%)</td>
<td>91</td>
<td>90</td>
<td>28</td>
<td>87</td>
<td>87</td>
<td>51</td>
<td>94</td>
</tr>
</tbody>
</table>

by the reaction of hydrazine with the corresponding ester precursors. Up to now, a lot of works have been done by the cyclization of hydrazides or their derivatives, mainly including alkyl, aryl and thio hydrazides, to prepare triazole derivatives.

2.2.1. Alkyl Hydrazides

It has been well investigated that alkyl hydrazides as an important class of effective building blocks for the preparation of nitrogenous heterocycles, especially for the synthesis of 1,2,4-triazole...
Scheme 25.

Scheme 26.

Scheme 27.

Scheme 28.

Scheme 29.

formate in refluxing methanol and following by addition of sodium methoxide via a succinct and easy operation of one-pot synthesis to conveniently produce N-nitrophenyl triazolone 80 with high yields of 76-86%, and subsequently the latter was treated by oxirane to generate Fluconazole analogues with excellent activities against the evaluated fungi (Scheme 30) [111].
It has been over the past decade that N-heterocyclic carbenes as important ligands for transition metal-based homogeneous catalysis have emerged in the field of asymmetric catalysis, and triazole derivatives with multiple nitrogen atoms have played important roles in asymmetric technology as chiral carbone ligands. The cycloaddition of N-isopropyl substituted hydrazide with imidoyl chloride was able to quantitatively yield chiral 1,4-disubstituted triazolium which could be further transformed into chiral [RhCl(N-HC)(COD)] catalyst by the coordination with [RhCl(COD)]2 (Scheme 31) [112].

2.2.2. Aryl Hydrazides

Aryl hydrazides as an important type of industrial materials exhibit higher reactivity than alkyl ones, and they easily perform cyclization reactions to produce 1,2,4-triazole derivatives. The highly reactive methyl thioamide was able to cyclize with substituted phenyl hydrazide by the catalysis of trimethylsilyl triflate/silver triflate (TMSOTf/AgOTf) to give the potent inhibitor of Hydroxysteroid Dehydrogenase Type 1 (HSD1) cyclobutane triazole which could conquer a cluster of health problems like hypertension, obesity and diabetes as well as dyslipidemias. However, no yields were reported for this transformation (Scheme 32) [113].

Triazole thiones display analgesic activity, and a lot of work has been directed towards development of new triazole thione derivatives as anti-inflammatory agents. Triazole thione as new type of potential analgesic compound with significant activity was successfully prepared by the cyclization of hydrazide, a sulfur containing phenyl derivative on phenyl ring in compound, with potassium thiocyanate and hydrochloric acid followed by cyclization of thiosemicarbazide. When compound was treated by car-

2.2.3. Thio Hydrazides

Thio hydrazides, including amino and thiol hydrazides, have been extensively employed as cyclization reactants for the construction of sulfur containing 1,2,4-triazole derivatives with intriguing properties.

2.2.3.1. Amino Thio Hydrazides

Amino substituted thio hydrazides have usually been served as general intermediates for the preparation of thio triazole derivatives, and a lot of achievements have been acquired such as anti-inflammatory phthalazine containing triazoles, anti microbial phenyl imidazole bearing thiazole-3H-1,2,4-triazole-3-thiones, anticonvulsant thiazole containing 1H-1,2,4-triazoles, antitubercular thiazole fused triazoles, antidepres-
Numerous researches have manifested that thio triazole derivatives should be associated with efficient antibacterial and antifungal activities [121, 126]. In continuation of ongoing interest in the development of new antimicrobial agents, sulfur containing triazoles have attracted much attention. The reaction of halobenzyl halide with thiosemicarbazide \( \text{A1} \) successfully produced halobenzyl hydrazine carbothioamide, and then the nucleophilic reaction with formic acid afforded intermediate \( \text{A2} \). The following cyclization under acid condition produced triazole thione \( \text{92a} \), and its further transformation provided the isomer triazole thiol \( \text{92b} \) in 73-82% yields. In the process of reaction conditions screening, it was found that the solvent and base played remarkable influence on the formation of compound \( \text{92} \) (Scheme 35). Notably, ethanol led to relatively high yields in contrast to acetonitrile which might be attributed to the good dissolvability of thiosemicarbazide in this solvent, but the presence of base resulted in low yields of target compounds due to formation of by-products [126]. This method provides a newly developed multicomponent procedure to prepare triazole thiol derivatives and triazole thiones with easy and convenient operation, short reaction time and high yields.

Thiocarbohydrazide \( \text{93} \) could undergo cyclization with 5-nitro-2-furoic acid through a one-step procedure to afford furane 4-amino-1,2,4-triazole-3-thiol \( \text{94} \) in 78% yield (Scheme 36). Antitumor precursor \( \text{94} \) as a lead compound was of much potentiality to be further modified by aromatic aldehydes, alkyl/aryl isothiocyanates or phenacyl bromides via condensation to afford thiazolazole or thiadiazine fused triazoles with strong cytotoxicity against hepatocarcinoma (Hep-G2) and human colon tumor (HCT-116) cell lines [127].

As is well known, acyl containing amino thio hydrazides can perform intramolecular cyclization under basic conditions to give functional triazole thione derivatives, and this synthetic procedure is widely employed for the construction of triazoles skeletons bearing special fragments [128-132] such as benzimidazoles, pyridazine, sulfinilamides and so on. The intramolecular cyclization of benzimidazolyl thio hydrazide \( \text{95} \), which was prepared by the reaction of hydrazide with methylisothiocyanate, successfully provided hybrid of triazole and benzimidazole \( \text{96} \) with potent antioxidant activity in the presence of sodium hydroxide (Scheme 37) [133]. The similar synthetic procedure was applied to prepare pyridazine substituted 1,2,4-triazoles which showed highly significant reduction in mean arterial blood pressure but with higher dose in comparison to standard drugs Hydralazine and Propanolol [134]. Moreover, a series of novel sulfonamide-1,2,4-triazolones (26-65%), triazole thiones (53-96%) and benzodioxane triazoles (96%) as well as phenyl triazoles were conveniently developed in the similar preparative method, and these intriguing molecules exhibited interesting bioactivities like antibacterial, antifungal and antitumor properties [135-137]. This type of synthetic strategy provides a fast (several minutes), facile and efficient method to access substituted 1,2,4-triazole thione derivatives [138-142].
Recently, epidemiological studies have shown that the highly selective COX-2 inhibitors have serious side effects in clinical use. In the search for new anti-inflammatory agents with low toxicity and little resistance, special attention has been paid towards a wide variety of heterocycles like pyridazinones, 1,3,4-thiadiazoles, especially 1,2,4-triazole thione derivatives. Therefore, the sodium bicarbonate catalyzed intramolecular cyclization of compound \(97\) was carried out which highly yielded the corresponding pyridazinone containing triazole thione \(98\) as anti-inflammatory agent with superior gastrointestinal safety (Scheme 38), and while the presence of acid resulted in pyridazinone thiadiazoles in 40-90% yields [143].

It is well known that the same starting materials can always lead to various types of products under diversified reaction conditions in synthetic chemistry, and this might be attributed to the different synthetic mechanisms. Bis-phenylsulfone containing thio hydrazide \(99\) could generate intramolecular cyclization when refluxed in sodium hydroxide solution and followed by treatment with hydrochloric acid solution to give triazole thiol \(100a\) and its tautomer triazole thione \(100b\) in overall yields of 62-80%. However, intramolecular cyclization in the presence of concentrated sulphuric acid and subsequent ammonia solution provided thiadiazoles in 74-92% yields (Scheme 39). It was noticeable that this transformation could proceed smoothly to produce triazole compound with yield up to 80% when the substituents \(R^1\) and \(R^2\) are Br and 4-OCF\(_3\) respectively [144].

**2.2.3.2. Thiol Thio Hydrazides**

The cyclization of thiol thio hydrazides with hydrazine hydrate has also attained the status of an important pathway in preparation of triazole derivatives. The investigation and application of this strategy have prepared several interesting 1,2,4-triazole-based compounds bearing both amino and thiol groups [145]. This type of synthetic method provides practical access to amino triazole thioles which may favorably react with 1,3,4-thiadiazoles or 1,3,4-thiadiazines to prepare new types of fused heterocyclic compounds with broad bioactive spectrum such as antimicrobial [146-149], anti-inflammatory, analgesic [150,151] as well as antiepileptic activity [152].

Naturally, the chemistry of 1,2,4-triazole derivatives and their fused heterocyclic ones has received considerable attention owing to their effective biological properties. Thiol thio hydrazide \(101\), a condensed product of hydrazide with carbon disulphide, reacted with hydrazine hydrate to efficiently provide anti-inflammatory precursor 4-amino-5-substituted-4\(H\)-1,2,4-triazole-3-thiol \(102\) in high yield of 85%, and the latter could be further treated by various aromatic carboxylic acids in phosphorous oxychloride to yield thiadiazole containing triazoles or by a series of phenacyl bromides to produce thiadiazines bearing triazoles in good yields of 80-86% (Scheme 40) [153].

Fluoroquinolone structure as an important type of pharmacodynamic fragment is a popular scaffold in lots of pharmacologically
active artificial and natural compounds. Many researches have modified the C-3 carboxylic group of fluoroquinolones to develop novel antitumor drugs. Cyclization of Ofloxacin thio hydrazide 103 with hydrazine hydrate at the catalysis of sodium hydroxide provided anticancer precursor quinolone triazole derivative 104 in 72% yield (Scheme 41). Further modification of this important intermediate successfully afforded the double functional compound bearing side chains of both Schiff and Mannich bases with excellent in vitro antitumor activity against the tested cell lines [154]. This research opens a new strategy to develop novel antitumor fluoroquinolone candidates from antibacterial analogs by introducing a triazole ring as bioisostere of the C-3 carboxylic group via convenient procedures.

Pyridine bridged thiol thio hydrazide 105 could also successfully generate molecular cyclization to produce pyridine bis-1,2,4-triazole 106 in 63% yield in the presence of excess hydrazine hydrate, and then subsequently was reacted with aromatic acid in the catalysis of phosphorus oxychloride to provide fused triazole derivatives which possessed large conjugated plane for accepting or transporting charge and could also be used as hole transport materials (Scheme 42). This method was frequently applied for the synthesis of bis-triazole compounds with large conjugated planes of high ionization or low electron affinities which could be used as good transferring holes materials in organic light emitting diodes (OLEDs) [155]. In same fashion, pyridine mono thiol thio hydrazides were also transformed into the corresponding triazoles, and could be subsequently glycosylated to afford glucoside bearing triazoles with good antibacterial and antifungal activities [156].

Various types of substituted hydrazides as starting materials have been extensively employed to construct functional triazole derivatives and a lot of remarkable progress has been acquired. It is foreseeable that more and more types of hydrazides including cyclic ones will be continuously served as reactants to prepare novel triazole derivatives with special properties, and the related researches will become increasingly active in future [157-160].

2.3. Cyclizations of Hydrazines

Hydrazines as raw materials of hydrazones and hydrazides can also be used to prepare triazole derivatives via direct cyclization with carbon containing compounds. The reaction of hydrazine with amidine 107, a substituted aniline with diphenyl cyanocarbonimidate, conveniently produced diamino triazole 108 which possessed higher selectivity to tyrosine kinase 2 (TYK2) than Janus associated kinase 1-3 (JAK1-3) (Scheme 43) [161]. This synthetic strategy is
Acyl amidines as important active building blocks have frequently appeared in biomolecules, and recently they have been found with ability to construct nitrogenous heterocycles [162]. The facile, practical and efficient one-pot reaction of acyl amidine 109 with hydrazine hydrate reliably provided potent PI3K inhibitor 110 with a special structure of thiophene triazole, but the reaction mechanism was not mentioned (Scheme 44) [163]. Another synthesis was the conversion of amides with N,N-dimethylformamide dimethyl acetal (DMF-DMA) at 100 °C to the corresponding ylideneamide, followed by the reaction with hydrazine to form desired triazole derivative 110. However, the yields for this cyclization step are not mentioned in the experimental part, and only the total yield for the totally synthetic scheme was indicated as 70% [164].

Compound 111, a coupled product of commercially available carboxylic acid with amidine, easily reacted with cyclohexyl hydrazine 112 in one-pot procedure under the catalysis of acetic acid to give 1,3,5-trisubstituted 1,2,4-triazole 113 (78%) as pharmaceutically active molecule (Scheme 45) [165]. The reaction optimization and substrate scope studies for this one-pot synthesis revealed that the incorporation of aryl and alkyl substituents at 5-position, and heterocycloalkyl group at the 3-position of triazole ring are viable substrates for this transformation [166]. This type of coupling reactions provides a practical synthetic pathway with substituent compatibility under mild conditions to produce considerable diversity of 1,3,5-trisubstituted 1,2,4-triazole skeletons.

Moreover, some aryl hydrazines are also employed as building blocks to construct 1,2,4-triazole derivatives. The mixture of phenylhydrazine 114 and N-cyanobenimidate 115, which was obtained by the reaction of inexpensive reagents aldehydes using cyanamide as nitrogen source and N-bromosuccinimide as oxidant, could proceed the cyclization of intermolecular C-N and C-O bonds by one-pot synthesis to afford 1,3,5-trisubstituted triazole 116 (82%) (Scheme 46) [167]. This synthesis could be further extended to the preparation of aniline substituted 1,2,4-triazoles in yields of 67-90% [71]. This method is an efficient one-pot procedure with the mild cyclization reaction of hydrazines to produce 1,2,4-triazole derivatives in good yields.

Noticeably, the one-pot multicomponent reaction (MCR) of substituted phenyl hydrazine 117, ammonium thiocyanate and acid chlorides could efficiently produce triazole-3-thione 118 in high yields under solvent free conditions at room temperature. A possible mechanism for this transformation was proposed that the reaction was started from the formation of isothiocyanate B1, followed by the addition of aryl hydrazine to construct B2, and subsequently cyclized to generate B3. The latter was converted to compound 118 by elimination of water. Continuous researches showed that the different types of substituents could also accomplish this cyclization in excellent yields, and this clearly pointed out that the substitution on benzene ring exhibited weak effects on the formation of target triazoles (Scheme 47) [168].

The discovery of new and safe anti-inflammatory drugs is becoming a challenge. It has been reported that phthalazine containing triazoles possessed anti-inflammatory potentiality, and this has attracted much attention to prepare phthalazine derived anti-inflammatory candidates. The intermolecular cyclization of phthalazine containing hydrazine 119 with cyanogen bromide provided fused amino triazole 120 in low yield of 30%, and subsequent O-alkylation with a series of alkanols or substituted phenols afforded anti-inflammatory 6-alkoxy(phenoxy)-1,2,4-triazolyl-3-amine (Scheme 48) [169]. Further researches are necessary to improve the low yields of this synthetic method.

Additionally, some other hydrazine derivatives like N-Boc compounds have also been used as reactants to prepare 1,2,4-
Recently, N-linked different heterocycles have received much attention because they are difficult to prepare under alternative conditions and represent previously unexplored heterocyclic cores. Fortunately, internal alkyne containing hydrazines were found to be able to undergo regioselective Ru-catalyzed cycloaddition of azide with alkyne to yield substituted hydrazine 1,2,3-triazole and then the resulting heterocycle was rapidly transformed into an unusual N-1,2,3-triazole functionalized 1,2,4-triazole (54%) by simple addition of formamide and anhydrous hydrogen chloride (Scheme 49). Further work displayed that these heterocyclic systems would be difficult to disconnect via alternative chemistry which demonstrated the significant promise of ynehydrazines for the preparation of N-linked bis-heterocycles [170].

2.4. Cyclizations of Guanidines

Guanidines as starting reactants have been widely used in organic synthesis and medicinal industry. Much literature has manifested that guanidines can be easily transformed into amino-1,2,4-triazole derivatives with high reactivity and intriguing properties.

Amino guanidine 123 could react with hot malonic acid by gradual addition to produce malonyl amino guanidine intermediate, and the latter underwent intramolecular cyclization in the presence of potassium hydroxide and subsequently acidified with concentrated hydrochloric acid to pH = 4-5 to give desired 5-amino-1H-1,2,4-triazole-3-acetic acid 124 in 65% yield. Further transformation of compound 124 could produce potential energetic material nitro triazole in yield of 70% (Scheme 50) [171,172]. Compound 123 could also condense with oxalic acid, and then performed cyclization to afford bis[3-(5-amino-1,2,4-triazolyl)] compound [173].

Guanidine derivative 125 was prepared via substitution of thioether by hydrazine derivatives in microwave oven and its purification was done by reverse phase HPLC (using acetic acid in water and acetonitrile as eluents) (Scheme 51). The intramolecular
cyclization of this compound under microwave irradiation successfully accessed amino triazole derivative 126. Experiments pointed out that substituents showed large effects on this transformation. When \( R_2 \) was 4-fluorobenzyl group, compound 126 was obtained in yields of 48-70%. In this case, when the substituent \( R_1 \) is 2,4-dichlorobenzyl group, this reaction gave the highest yield up to 70%. However, if \( R_2 \) was benzyl or alkyl groups, the conversion yields would decrease to 34-65% [174].

Intramolecular cyclization of compound 127 in ethanol provided benzylthio substituted 1,2,4-triazole 128 in good yield with the concomitant expulsion of acetone and aniline. Compound 128 was found to have potentiality to be served as inhibitor of the methionine aminopeptidase-2 (Co\(^{2+}\)-MetAP2) enzyme (Scheme 52) [175]. Although this synthetic route is easy to perform, however, this reaction is limited because the substituted aniline guanidine intermediates are difficult to prepare.

### 2.5. Cyclizations of Other Compounds

Some other compounds like nitriles and amidines etc. can also proceed cyclization to generate 1,2,4-triazole derivatives. The reaction of benzonitrile with isoquinoline amidine 129 in the presence of copper ions formed the coordinated intermediate \( C_1 \), subsequently, copper complex promoted nucleophilic attack of amino isoquinoline on the nitrile to provide amidine \( C_2 \), then oxidative cyclization was developed using molecular oxygen (air at 1 atm) as oxidant which was induced by copper ions to give isoquinoline triazole 130 that was known as a potent nonhormonal antifertility agent, and the water was produced as the sole theoretical by-product (Scheme 53). Further studies of substituents effects demonstrated that the electron withdrawing groups like halogens and trifluoromethyl group on benzene ring gave the corresponding triazoles with good yields, while benzonitrile was substituted by methoxy group, the transformation efficiency was quite low to 55%. Acetonitrile could also be employed instead of benzonitrile to prepare triazoles in similar yield (52%) [176].

Cyclization of diethyl azodicarboxylate (DEAD) 131 with the N-protected imine 132 in the presence of triphenylphosphine was able to produce triazole derivative 133a in yield of 23% and its isomer 133b with relative high yield of 58% when the molar ratio of 132, DEAD and triphenylphosphine was 1:1.5:1.5. Experiments revealed that the reactant concentration highly influenced the formation of products, and the high concentration resulted in the formation of products in almost quantitative yields (75% and 25% respectively). The possible mechanism was shown in (Scheme 54).

Initially, the reaction of triphenylphosphine with DEAD 131 produced the zwitterionic intermediate \( D_1 \), which underwent nucleophilic addition of N-Boc protected imine to form intermediate \( D_2 \). The intramolecular addition of intermediate \( D_2 \) yield intermediate \( D_3 \) and the latter subsequently generated the elimination of triphenylphosphine oxide to give product 133a [177].

The tremendous success of cyclization to access 1,2,4-triazole derivatives has prompted numerous efforts towards the cyclizations
of hydrazines and their derivatives. So far some good preparative methods for triazole derivatives have been successfully found and established, in particular, the cyclization of hydrazones, hydrazides and guanidines as well as their derivatives have already shown large prospects in preparation of triazoles. Undoubtedly, cyclization or cycloaddition preparative methods will continue to play important roles in the developments of various sorts and varieties of 1,2,4-triazole derivatives with novel structures and extensive potential applications.

3. TRANSFORMATIONS OF HETEROCYCLIC COMPOUNDS TO CONSTRUCT TRIAZOLE RING

The interconversions of heterocyclic compounds represent another alternative strategy to prepare some special structures which are difficult to develop through traditional strategies in heterocyclic chemistry. Up to now, some rare triazole derivatives have been successfully prepared via the transformations of heterocycles including five- and six-membered ones, and this type of synthetic strategy has contributed practical methods to construct some special 1,2,4-triazoles. Among these reported heterocycles, oxazoles and azines as transformation precursors to prepare 1,2,4-triazole derivatives have been paid special attention.

3.1. Transformations of Five-Membered Heterocyclic Compounds

Recently, rearrangements of five-membered heterocycles such as oxadiazoles, oxazolones, tetrazoles and thiazoles to prepare 1,2,4-triazole derivatives have attracted much interest in synthetic chemistry.
**Table 4. Effects of Different Factors on the Formation of Compounds 135a-f**

<table>
<thead>
<tr>
<th>Compound 135</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
<th>e</th>
<th>f</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>Cl</td>
<td>OCH₃</td>
<td>(CH₃)₂NH₂</td>
<td>Cl</td>
<td>(CH₃)₂Cl</td>
<td>Cl</td>
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<tr>
<td>Ar</td>
<td>Ph</td>
<td>Ph</td>
<td>Ph</td>
<td>4-CH₃Ph</td>
<td>Ph</td>
<td>4-ClPh</td>
</tr>
<tr>
<td>Mole Ratio</td>
<td>100</td>
<td>84</td>
<td>57</td>
<td>100</td>
<td>12</td>
<td>100</td>
</tr>
<tr>
<td>Yield (%)</td>
<td>90</td>
<td>69</td>
<td>51</td>
<td>85</td>
<td>8</td>
<td>75</td>
</tr>
</tbody>
</table>

Oxadiazoles, including 1,2,4-oxadiazoles and 1,3,4-oxadiazoles which possess various bioactivities like antibacterial, antifungal and antitumor potencies [178], have relatively high reactivity due to the inductive effect of oxygen atom in the oxadiazole ring, and they have been investigated very well to transform into more stable heterocycles, especially 1,2,4-triazole derivatives [179-187]. In recent years, the prepared triazoles via rearrangement of oxadiazoles usually exhibited wide applications in medicinal chemistry especially as antitubercular [188] and antiproliferative agents [189], and also in supramolecular chemistry as progesterone receptors and ligands of coordination polymers [64,190,191].

As anticipated, 1,2,4-oxadiazole 134 could undergo ring opening and subsequent closure with hydrazine via two pathways to produce amino 1,2,4-triazole 135. In path a, the initial nucleophilic attack on the C(5) of the oxadiazole ring caused ring-opening into intermediate E₁, and subsequent ring-closure of the former C(3) of the oxadiazole with loss of the leaving group led to hydroxyl aminotriazole E₅; and in path b, the initial attack at the C(3) of the oxadiazole 134 generated the dihydroxadiazole derivative E₂, and then nucleophilic attack at C(5) followed by ring-opening and ring-closure involving either the intramolecular 3-hydrazino moiety or another external hydrazine molecules to produce compound E₅, which is then reduced into amino triazole 135 (Scheme 55) [192].

Optimization of reaction conditions found that the mole ratio (hydrazine/Compound 134) had remarkable influence on this transformation and the type of C(5) substituent exhibited few effects on this rearrangement (75-90%). As shown in (Table 4), when the reactant mole ratio was up to 100, the yields of target compounds were largely increased, and while it was 12 times hydrazine excess, the yield was quite low to 8% for product 135e. Indeed, the observed reactivity of 134 seemed to be strongly dependent on the leaving group ability of the C(3) substituent R rather than on its electronic effect. Moreover, it was also found that the substituents on benzene ring had some influences on this transformation, and non-substituted benzene gave the highest yield of 90%, while 4-CH₃ and 4-Cl groups produced lower yield with 85% and 75% respectively (Table 4).

Dichlorophenyl 1,3,4-oxadiazole 136 as the isomer of 1,2,4-oxadiazole could also generate ring transformation by the treatment of 2-methylbenzyl amine to produce triazole derivative 137 which was easily separated from by-products (Scheme 56). The conversion yield did not exceed 50%, but it was worthy to notice that compound 137 may be further converted into the corresponding salt which had sufficient solubility for pharmacokinetic and efficacy studies in vivo, and exhibited anti-nociceptive activity in the rat of neuropathic pain [193].

Oxazolones are an important class of electron rich heterocycles and the presence of electronegativity nitrogen atom decreases the electron density of the entire system, especially π electron density on the C-2 position, which is easily attacked by nucleophiles and results in the ring-opening, following by ring-closure to produce other heterocyclic compounds [36]. Electrophilic attack of oxazolone 138 to azodicarboxylate led to the formation of intermediate F₁ in acetonitrile, subsequently underwent ring opening to generate nitrilium intermediate F₃ which proceeded the cycloaddition upon nucleophilic attack by the other nitrogen of azodicarboxylate via a 5-endo-dig-type ring closure to give the expected triazole derivative 139 without the assistance of any catalysts at room temperature. Further decarboxylation and aromatization in catalysis of alcoholic sodium hydroxide in refluxing ethanol gave triazole compounds (Scheme 57). The in-depth investigation of the reaction progress revealed that substituents highly affected the transformation efficiency. This conversion proceeded smoothly in very good yields for H, 4-F, and 4-OCH₃ moieties of R¹ especially the production of 139a with yield up to 100%. The transformation was significantly hampered when the oxazolones were substituted by the electron withdrawing 4-NO₂ moiety. The R² and R³ positions were substituted by CH₃, Et, i-Pr or Bn moieties, all provided the triazoline products in very good yields (Table 5) [194].
Moreover, the rearrangement of tetrazole 140 under participation of imine 141 in toluene was able to generate phenyl triazole 142 with good activity against 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) enzymes. The mechanism of this transformation was considered to involve the nucleophilic attack of the tetrazole ring on the imidoyl chloride of compound 141 followed by the loss of nitrogen atom (Scheme 58). The structure activity relationship demonstrated that the introduction of 2-Cl and 2-CF$_3$ groups could highly increase the activity which was mainly because the 2-substitution forced the phenyl moiety out of the triazole ring and helped it to be more efficiently to fill into the hydrophobic pocket of the enzyme active site [195].

3.2. Transformations of Six-Membered Heterocyclic Compounds

Six-membered heterocyclic compounds can also be readily attacked by nucleophilic moiety to be transformed into triazole containing compounds accompanying with reduction of atom in the rings, during which azines as representative ones have been investigated very swell [36]. The nucleophilic attack of phenyl hydrazine proceeded at position 2 of pyrimidinium 143, and subsequent participation of the second nitrogen atom of hydrazine formed 1,2,4-triazole 144 in 31-43% yields (Scheme 59), and this type of transformation reaction brought an excellent addition for the synthesis of 1,3,5-trisubstituted triazoles although the yields were relatively low [196].

The transformation of 1,2,4,5-tetrazine compounds also is a powerful synthetic pathway to access triazole compounds. By the catalysis of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 3,6-substituted 1,2,4,5-tetrazine 145 may be transformed into the corresponding 3,5-substituted 1,2,4-triazole by the attack of nucleophilic substituted phenyl acetonitrile. Experiments showed that the substituents on benzene ring had a large effect on the ring opening of 145 and formation of triazole ring. In comparison with 146b, either the introduction of 4-Br substituent in R$_1$ of compound 146a or the substitution of 2-NO$_2$ group in R$_2$ of 146c would decrease yields low to 43% and 51% respectively, further introduction of 5-CH$_3$ moiety led to a lower yield of 146d (36%) (Scheme 60) [197].

The transformations of heterocycles are an important synthetic strategy for the construction of structurally special 1,2,4-triazole derivatives. Though some synthetic technologies such as photocatalysis and microwave-assistance have vastly expanded the application scope of this approach, the difficult preparation of precursor heterocycles has largely hampered their transformations to access triazoles to some extent.

<table>
<thead>
<tr>
<th>Compound 139</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
<th>e</th>
<th>f</th>
</tr>
</thead>
<tbody>
<tr>
<td>R$_1$</td>
<td>H</td>
<td>H</td>
<td>4-NO$_2$</td>
<td>4-OCH$_3$</td>
<td>4-F</td>
<td>H</td>
</tr>
<tr>
<td>R$_2$</td>
<td>CH$_3$</td>
<td>CH$_3$</td>
<td>CH$_3$</td>
<td>CH$_3$</td>
<td>CH$_3$</td>
<td>Bn</td>
</tr>
<tr>
<td>R$_3$</td>
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<tr>
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<td>99</td>
<td>50</td>
<td>85</td>
<td>98</td>
<td>82</td>
</tr>
</tbody>
</table>

Table 5. Effects of Substituents on the Formation of Compounds 139a-f
4. SUBSTITUTIONS ON 1,2,4-TRIAZOLE RING

The highly reactive unique three-nitrogen five-membered aromatic heterocycle is readily modified by various types of functional groups to generate novel 1,2,4-triazole derivatives with multiple purpose applications. In fact, the structural modification of 1,2,4-triazole ring has been one of the most convenient and efficient strategies to build new triazole molecules with a variety of substituents and has been developed vigorously and increased actively. The lone pair of electrons in nitrogen atoms make 1,2,4-triazole ring easily proceed N-alkylation, N-arylation, N-acylation and N-quaternization with a variety of electron deficient centers to efficiently prepare 1,2,4-triazole-based derivatives. However, the structural modifications of carbon atoms in triazole ring are relatively seldom reported mainly involving C-substitution of triazole ring because of their inertia properties [198, 199].
4.1. N-Alkylation of 1,2,4-Triazole Ring

N-alkylation modifications of 1,2,4-triazole ring have been being prevalent synthetic methods in developing bioactive triazole compounds, which not only exhibit a variety of biological activities, but also are widely used in supramolecular chemistry like artificial cation and anion receptors as well as luminescent and magnetic materials [3].

4.1.1. N-Alkylation of 1H-1,2,4-Triazole

1,2,4-Triazole exhibits weak acidity with three nitrogen atoms in the aromatic azole ring as well as a tautomeric equilibrium with 4H-1,2,4-triazole. In the presence of base, both 1H-1,2,4-triazole and 4H-1,2,4-triazole display five resonance forms (G1, G2, G3, G4 and G5). Among them, patterns G1 and G3, G5 and G4 are the same forms respectively. Moreover, patterns G1, G2 and G4 are more stable than patterns G3 and G5 [200]. Therefore, N-alkylation of 1,2,4-triazoles can yield two products, and the N-1 alkylated products are the predominant ones in the presence of weak base (Fig. 3).

A large amount of literature has manifested that N-alkylation reactions of 1H-1,2,4-triazole with halides, oxiranes and alcohols as well as alkynes mainly produce the 1-substituted products, accompanying with a small amount of 4-substituted by-products [2]. Currently, N-alkylation of 1,2,4-triazole ring is still one of the most convenient and common ways to prepare new triazole derivatives [201, 202].

4.1.1.1. N-Alkylation with Halides

As reported that the combination of 1,2,4-triazoles with other functional fragments such as sulfamides, benzimidazoles, piperazines, thiazoles as well as 1,2,3-triazoles [203-209] via N-alkylation reaction has been widely employed to prepare 1,2,4-triazole derivatives with broad spectrum and good bioavailability [210, 211]. Alkyl halides with high reactivity are of great significance in synthetic chemistry for N-alkylation to prepare diverse functional molecules, especially in developments of bioactive 1,2,4-triazoles [212,213].

Carbazole and its derivatives possess desirable electronic and charge transport properties as well as large π-conjugated system, and these special structural characteristics endow them to have unique functional properties and biological activities [211]. More importantly, their structures are easily modified to afford newly bioactive compounds. The conjunction of triazole with carbazole ring into one molecule may generate a novel type of bioactive compounds. N-alkylation of 1,2,4-triazole with carbazole bromide 147 was able to be carried out in acetonitrile at 45 °C to provide triazole derivative 148 in high yields of 76-91%. Experiments showed that the carbazole aralkyl bromides gave higher yields than alkyl ones. Particularly, the high reactivity of carbazole derived p-benzyl bromide made the corresponding yield up to 91%, but the hexyl substituted one gave the lowest yield of 76% (Scheme 61) [214].

A large number of researches have focused on further investigation of Fluconazole in order to broaden its antimicrobial spectrum and increase its therapeutic indexes [215-217]. N-Alkylation of 1H-1,2,4-triazole with amine derived dibromide 149 in the presence of potassium carbonate afforded novel tertiary amine type of Fluconazole analogues bis-triazole 150a-c in good yields ranging from 76% to 84%. Researches found that the types of substituents and substituted patterns on benzene ring had little effect for this transformation, but they displayed remarkable influence on the bioactivity [218, 219]. The reaction of 1H-1,2,4-triazole with amine dibromide 149 in the mole ratio of 1:1 could also be controlled to produce mono-triazole derivative 151 in moderate yields of 40-63%. Further reaction of compound 151 with berberrubine gave berberine triazole 152 with excellent antimicrobial activities which was 2- and 16-fold more potent activity than the reference drugs Chloromycin and Berberine against MRSA respectively, and equipotent to Norfloxacin (MIC = 8 μg/mL) (Scheme 62) [220,221]. This strategy provides a practical way for the construction of completely new type of Fluconazole analogues to explore the ideal lead compounds for clinical therapy [222].

The combination of coumarins with some nitrogen heterocycles such as pyrrole and thiazole can effectively increase the bioactivity and broaden antimicrobial spectrum [223-226]. Recently, the introduction of triazole ring into coumarins has also been reported to display excellent bioactivity. Reaction of 1,2,4-triazole with coumarin dibromide 153 successfully provided coumarin bis-triazole 154 in yields of 71-83% (Scheme 63). The bridged linkers exhibited little effect on the formation of bis-triazole 154, but showed an obvious influence on antimicrobial efficacy [227]. This preparative method provides an easy, convenient and economic synthetic procedure with a large potentiality for further development of coumarin triazole derivatives as antimicrobial candidates for clinic.

Piperazine ring is an attractive pharmacological scaffold present in various potent marketed drugs. Because of easy modifiability, proper alkality, water solubility, the capacity for the formation of hydrogen bonds and adjustment of molecular physicochemical properties, piperazine ring has been frequently employed in design and development of new drugs [228-231]. Compound 155 is a piperazine-based chloride which was obtained by the coupled reaction of chloroactyl chloride with 1-((4-chlorophenyl)(phenyl)meth-
thyl)piperazine, and could also successfully generate N-alkylation with 1H-1,2,4-triazole in the presence of anhydrous potassium carbonate to access piperazine triazole with remarkable antimicrobial efficacy and broad antimicrobial spectrum (Scheme 64) [232].

Substituted or unsubstituted benzyl halides as highly active alkyl reactants are very easy to perform the N-alkylation of triazole. Benzofuran containing benzyl chloride 157 was obtained by the treatment of benzofuran methanol with thionyl chloride, and could react with 1,2,4-triazole via N-alkylation to provide potential anticancer aryl triazole 158 (27-85%) (Scheme 65). The type of substituent R showed remarkable influence on the yields of this reaction, and the presence of methoxy group gave the high yield up to 85%, while nitro, methyl and trifluoromethyl derivatives produced the target compounds with quite low yields (lower than 30%), and the influential factors on this transformation were under investigation (Table 6) [233].
isomers of antifungal compounds with excellent anti-
Aspergillus
latter could be further modified with indazoles to afford two new
compounds successfully provided triazole derivative
H
bromide and subsequent epoxidation, with 1
pound
[5,10]. In the presence of sodium hydride, reaction of oxirane com-
clinically useful antifungal azoles with broad bioactive spectrum
promotes the development of its derivatives to search for new and
activity.
but they displayed remarkable influences on the antimicrobial
benzene ring should have no obvious effect on this transformation,
[237]. The experimental results showed that the substituents on
then epoxidation with trimethyl sulfoxonium iodide (Scheme
Friedel-Crafts acylation, N-alkylation with 1
H
with epoxide
159
66).

Scheme 66.

4.1.1.2. N-Alkylation with Oxiranes
Oxirane compounds, a special class of three-membered ring
systems, are easy to open ring by nucleophiles to prepare intriguing
organic molecules. Especially in the developments of Fluconazole
derivatives, oxirane compounds have been extensively employed
for the preparation of tertiary alcohol fragments [234, 235].
Fluconazole 160a as a clinical antifungal drug with good activ-
ity, safety profile and pharmacokinetics has been the first choice to
treat infections caused by Candida albicans and Cryptococcus neo-
forms [236]. Its preparation including the synthesis of its analogs
160b-c (19%) was performed through the N-alkylation of triazole
with epoxide 159 which was obtained from halobenzene via
Friedel-Crafts acylation, N-alkylation with 1H-1,2,4-triazole and
then epoxidation with trimethyl sulfoxonium iodide (Scheme 66)
[237]. The experimental results showed that the substituents on
benzene ring should have no obvious effect on this transformation,
but they displayed remarkable influences on the antimicrobial
activity.

The poor efficacy of Fluconazole against Aspergillus infections
promotes the development of its derivatives to search for new and
clinically useful antifungal azoles with broad bioactive spectrum
[5,10]. In the presence of sodium hydride, reaction of oxirane com-
ound 161, prepared by treatment of amide with phenyl magnesium
bromide and subsequent epoxidation, with 1H-1,2,4-triazole suc-
cessfully provided triazole derivative 162 in 61% yield, and the
latter could be further modified with indazoles to afford two new
isomers of antifungal compounds with excellent anti-Aspergillus
fumigatus activity (MIC_{90} = 0.25-4 \mu g/mL) which were 32- to 512-
fold more potent than Fluconazole (Scheme 67) [238].
Flutriafol as a broad spectrum triazole fungicide is widely em-
ployed for the control of many cereal diseases, and researches have
demonstrated that (+)-isomer is more active than the (-)-isomer.
Therefore, the development of Flutriafol in enantiopure form is of
great interest. Fluorophenyl epoxide 163 was obtained by the selec-
tive tosylation of diol with p-toluenesulfonyl chloride (TsCl) and
subsequent treatment by DBU. Nucleophilic reaction of compound
163 with 1,2,4-triazole successfully produced antimicrobial flutria-
ofol triazole 164 in yield of 77% (Scheme 68) [239]. This synthetic
method has been widely employed for the preparation of potent
chiral triazole fungicides.

4.1.1.3. N-Alkylation with Alcohols
Generally, hydroxyl group is usually difficult to leave and can
not be easily replaced in organic synthesis. However, in certain
conditions, N-alkylation of 1,2,4-triazoles with alcohols can suc-
cessfully proceed to generate new triazole derivatives.
A simple and one-stage method for N-alkylation of 3,5-
disubstituted 1H-1,2,4-triazole with salicyl alcohol was reported in
high yields. Salicyl alcohol was firstly transformed into o-
methylenequinone H1, followed by treatment with triazole deriva-
tive 165 to give alkylation product H2, and then underwent in-
tramolecular cyclization to afford triazole fused benzoxazine 166 in
refluxing DMF (Scheme 69) [240]. This effective method can be
served for the preparation of novel triazole fused derivatives.
Reaction of adamantane 167 with ammonium nitrate in sulfuric
acid readily yielded alcohol intermediate 168, and the latter could
further react with 1,2,4-triazole to give the potential antiviral ada-
mantyl triazole 169 in moderate yields (43-67%) (Scheme 70).
Researches found that the substituent R1 of compound 168 could
affect the yields to some extent. The -NH2 group was favorable for
the transformation with yield up to 67% [241]. This reaction pro-
vides a practical synthetic route for the preparation of triazole ada-
mantanes with large steric hindrance to overcome the serious amin-
tadine/rimantadine resistance of influenza viruses.

<table>
<thead>
<tr>
<th>Compound 158</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
<th>e</th>
<th>f</th>
<th>g</th>
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<td>CF3</td>
<td>Et</td>
</tr>
<tr>
<td>Yield (%)</td>
<td>83</td>
<td>80</td>
<td>85</td>
<td>73</td>
<td>30</td>
<td>27</td>
<td>28</td>
<td>77</td>
</tr>
</tbody>
</table>

Scheme 67.

**Table 6. Effects of Substituents on the Formation of Compounds 158a-h**
Thionyl bis-triazole can also be employed to N-alkylate with alcohols to produce novel triazole derivatives [242,243]. Reaction between compound 170 and N,N'-thionyltriazole 171 successfully afforded potential CYP26 inhibitor 1,2,4-triazole derivative 172 (Scheme 71) [244]. This method was easier to perform than that shown in (Scheme 65). Surprisingly, the yields of benzofuran phenyl triazoles are highly affected by the substituents on benzene ring far from reactive site. The isopropyl substituent gave the best yield up to 78%, while n-propyl group gave the lowest yield of 2% (Table 7). It is displayed that the electron rich density of substituents was favorable for this transformation and the short chain made this reaction perform smoothly.

**4.1.1.4. N-Alkylation with Alkenes**

Michael addition as one of the most important organic reactions has been widely employed to prepare various types of interesting compounds via formation of C-Z bonds (Z = C, N, O, S, etc.). α,β-Unsaturated aldehydes are also able to be employed in N-alkylation of triazole compounds via Michael addition [245]. The reaction of 2-butenal with 1H-1,2,4-triazole in the presence of benzoic acid and catalyst 173 could successfully produce triazole derivative 174, and the latter was reduced by sodium borohydride and subsequently reacted with acyl chloride to prepare a series of antifungal benzoate 1,2,4-triazoles in total yields of 53-91%. Experiments showed that electron donating methyl group on benzene ring was favorable for this transformation with the excellent yield up to 91%, and also the unsubstituted one gave good yield (72%), while the presence of electron withdrawing chlorine decreased the yield low to 53% (Scheme 72) [246].

Ionic liquids have been recognized as attractive candidates for new type of good propellants [247] and explosives [248,249] be-

**Scheme 68.**

**Scheme 69.**

**Scheme 70.**

**Scheme 71.**
cause of several ideal features as energetic materials such as low vapor pressures, broad liquid ranges, low melting points and so on. More importantly, the unique functional nature of ionic liquids permits the independent modification of ions in their structures \[250\]. Great interest is directed towards triazole ionic liquids in combination with tetrazoles due to their excellent energetic properties. The reaction of triazole with acrylonitrile in the presence of triethylamine effectively produced 1-(2-cyanoethyl)-1,2,4-triazole \[175\], and further transformation with sodium azide afforded triazole containing tetrazole salt \[176\] which could be served as excellent ionic liquid (Scheme 73) \[251\]. This synthetic strategy has opened a new direction to develop novel diheterocyclic energetic ionic liquids.

The N-alkylation of amino triazoles with unsaturated esters affords different products. Reaction of 3-amino triazole with diethyl benzylidenemalonate in refluxing methanol occurred in triazole ring not in amino group, which provided the product \[177a\] and isomer \[177b\] with low yields of 28% and 10% respectively, and the structures of the obtained compounds were clarified by X-ray crystallography (Scheme 74) \[252\]. Further works for this reaction are necessary to improve the yields of desired products.

### 4.1.1.5. N-Alkylation with Other Compounds

Some other compounds such as aldehydes, quaternary ammonium salts, esters and so on can also perform the N-alkylation of triazoles. The one-pot N-alkylation reaction of 4-methoxybenzaldehyde and methyl acetoacetate with amino 1,2,4-triazole could efficiently give pyrimidine fused triazole compound \[178a\] in 46% yield and its trace isomer \[178b\] (Scheme 75) \[253\]. This reaction exhibits some advantages with convenience, good selectivity and easy operations \[254\].

Quaternary ammonium salts have also been found to successfully perform N-alkylation with triazole, because of the easy cleavage of C-N bond in the presence of strong electron withdrawing permanent positive charge. The reaction of 3-isoxazolyl triazole \[179\] with pyrimidine-2-yl-trimethylammonium chloride \[180\] could generate N-alkylation in acetone to efficiently produce compound \[181\] with much potentiality as pesticide in agriculture production (Scheme 76) \[255\].

Diethyl sulfate as alkylation agent is scarely investigated due to its high toxicity. However, currently its high reactivity has attracted increasing interest. N-alkylation of nitro triazole with diethyl sulfate successfully proceeded to give N(2)-ethyl substituted nitro triazole.
and N(4)-substituted isomer in overall yields of 53-73% (Scheme 77). Researches demonstrated that when dimethyl sulfate was employed as alkylation agent, this reaction would give low yields of target compounds (26-45%) [256].

As is well known, glycosides with high reactivity have been widely used in organic synthesis and drug design [257]. Reaction of tetra-ester /g1/-D-xylopyranose 183 with dihalo triazole under activation of boron trifluoride effectively provided glycosyl triazole 184 in 53-71% yields, in which 3,5-dibromo-1H-1,2,4-triazole gave the highest yield up to 71% (Scheme 78). Further researches showed that compound 184 could undergo further C-alkylation to give the corresponding C-alkylated products [258]. This method opens a new synthetic direction to achieve the glycose containing triazole derivatives via efficient N-alkylation.

4.1.2. N-Alkylation of Thio 1,2,4-Triazoles

Mannich reaction has been playing an important role in developing biologically active compounds because of its convenient operations, mild reaction conditions and so on. Numerous works have been directed towards aminomethylation of formaldehydes and development of interesting molecules [259, 260], especially Mannich reaction of heterocycles via N-alkylation has been attracting special interest [261,262]. Multicomponent Mannich reaction of 1,2,4-triazole-3-thione 185, morpholine and formaldehyde was performed in ethanol to give antibacterial triazole thione 186 with good yields of 79-87% (Scheme 79) [263]. All the substituents on benzene ring which were far away from the reaction site displayed weak influence on the formation of triazole derivatives.

Recently, some clinical drugs like Itraconazole containing both piperazine and azole rings are prevalent antifungal agents which have been playing important role in the treatment of microbial infections. This promotes much effort towards the combination of different heterocyclic rings with unique properties into one molecule to explore bioactive molecules. Bis-triazole compound 187 was treated by formaldehyde and piperazine derivative to favorably produce antimicrobial piperazine bis-triazole 188 by a facile Mannich reaction in DMF (Scheme 80) [264].

In all, Mannich reaction with convenient operations, mild conditions and good yields has provided an efficient pathway to access aminomethyl 1,2,4-triazole derivatives, and this method will continuously be one of important active topics in developing diverse triazoles with special functional applications especially bioactive medicinal compounds.

4.2. N-Arylation of 1,2,4-Triazole Ring

It is well known that N-arylation of 1,2,4-triazole ring is usually difficult to perform due to the relatively weak reactivity of aryl compounds. However, N-arylation of triazole ring with aryl halides has been successfully carried out under relatively harsh conditions
such as high temperature, high pressure and so on. Notably, the presence of strong electron withdrawing groups on aromatic ring and special catalysts make this transformation become relatively easier [265].

Generally, fluorine atom which is directly linked to the benzene ring is particularly difficult to be substituted. However, if the electron withdrawing groups are directly linked with the benzene ring, this reaction will become very easy. In the presence of potassium carbonate, an environmentally benign nucleophilic substitution of fluorine atom in 4-fluorobenzaldehyde with 1,2,4-triazole could readily occur and efficiently produce N-substituted phenyl triazole in 72% yield. Compound 189 proceeded further cyclization with 3,5-difluorobenzene-1,2-diamine via a fast, highly efficient, eco-friendly and catalyst free chemical transformation to afford benzimidazole containing 1,2,4-triazole compound 190 with good antitubercular activity (Scheme 81) [266].

In comparison with fluorine atom, bromide was easy to be substituted generally. The reaction of 1,2,4-triazole with sulfonamide containing aryl bromide 193 using tris(dibenzylideneacetone) dipalladium (Pd2(dba)3) as catalyst via a mild and easy operation smoothly produced sulfonamide triazole derivative 194 with potency as inhibitor of 11β-Hydroxysteroid Dehydrogenase Type 1 (11β-HSD1) (Scheme 83). In this reaction, the fluorine atom was not substituted, this was probably attributed to the existence of the electron donating piperazine moiety at the para position [268]. Continuous researches found that replacement of catalyst Pd2(dba)3 by copper iodide was favorable for the N-arylation reaction with largely increased yields up to 81-98% [269].

Iodine containing compounds as important reactants are usually used to couple different fragments to build difunctional molecules due to the easily leaving reactivity of iodine atom. They have been frequently employed to perform N-arylation of 1,2,4-triazole ring to prepare interesting ionic liquids. Coupling reaction of iodobenzene with 1,2,4-triazole under the catalysis of cuprous oxide efficiently afforded 1-phenyl-1H-1,2,4-triazole 195 which could be used to constitute a new generation of 1,2,4-triazolium-based ionic liquids with a high degree of flexibility (Scheme 84) [23]. This reaction is an efficient method with good yields and easy operations for the preparation of phenyl triazoles.

Deoxyuridines play a vital role in the epigenetic regulation of genetic information and in the control of many cellular processes.
4.3. N-Acylation of 1,2,4-Triazole Ring

The N-acylation reaction of 1,2,4-triazole ring is an easy synthetic method to prepare acyl triazole derivatives. This type of preparative strategy with good reactivity has been extensively used in practical synthesis. Amino triazole is a commercial reactant and is often used to perform N-acylation with acyl halides for the preparation of ring acylated products rather than the amino acylated ones. The reaction of amino triazole 198 with (un)substituted benzoyl chloride at room temperature efficiently gave the acylation product anti-inflammatory 1-benzoylated-1,2,4-triazole 199 in 63-75% yields (Scheme 86), and the electron donating or withdrawing groups on benzene ring displayed little effect on the N-acylation of triazole ring. Interestingly, compound 199 could take place thermal rearrangement at 200-250 °C to give the amino acylated 1,2,4-triazole derivatives [171].

Triazole derivatives with special properties have attracted much attention for the development of anti-inflammatory drugs. The N-acylation of diamino triazole 200 with (un)substituted benzoyl chlorides efficiently produced potential anti-inflammatory compound 201a and its trace isomer 201b in total yields of 60-80%. Further researches are necessary to elucidate the effect of substituents on this reaction (Scheme 87) [161].

4.4. N-Quaternization of 1,2,4-Triazole Ring

Many researches have shown that triazoliums as the N-quaternization products of triazole ring possess extensive potentiality as energy materials, ionic liquids, artificial receptors etc. [271, 272]. Particularly in medicinal chemistry, the permanent positive charge rigid triazolium ring can easily form hydrogen bonds, accept electrons and produce electrostatic interaction with biological target sites leading to the enhancement of water solubility and membrane permeability, and thereby improving biological efficiency and broadening antimicrobial spectrum. Therefore, the transformation of triazoles into triazoliums has been becoming an important strategy for the preparation of triazolium medicinal drugs [273-277].

Triazoliums are very easy to prepare. For example, 1H-1,2,4-triazole could react with the highly reactive α-bromoketone 202 to
provide the N-alkylated product, and subsequently underwent N-quaternization of 1,2,4-triazole ring to successfully give triazolium in 49% yield. Bioactivity screening found that mono-triazolium bromide gave excellent antimicrobial activities with broad bioactive spectrum, and its anti-\textit{Saccharomyces cerevisiae} activity was 8-fold more potent than that of reference drug Fluconazole (MIC = 32 \mu g/mL) (Scheme 88) [278].

Naphthalimides with strong hydrophobicity and desirable large \pi-conjugated backbone could easily interact with various active sites in biological system via non-covalent forces to exhibit diversely biological activities. Recently, much effort has been directed toward naphthalimide derived compounds as medicinal agents. Experiment results demonstrated that naphthalimide containing triazole (MIC = 32 \mu g/mL) could be easily subjected N-quaternization of triazole ring with (un)substituted benzyl halides to afford triazolium product with improved water solubility and good antimicrobial activity (MIC = 1-32 \mu g/mL) (Scheme 89), and the substituents had little effect on the formation of triazolium ring [279].

Some bis-triazoliums with two positive charge groups are also successfully prepared by the N-quaternization of triazole ring. The mono-triazole reacted with a series of dihalides, which were commercially available or were prepared by conventional method via bromination of the corresponding precursors, via N-quaternization to readily produce bis-triazolium in good yields of 74-95%. Notably, the reaction temperature obviously affected the formation of target compounds, and only when the temperature was controlled above 80 °C, this reaction would proceed smoothly (Scheme 90) [280, 281].

The poor water solubility of clinical drug Fluconazole highly precludes its development and utilization as antifungal agent, thus much work is directed towards its further structural modifications for water soluble improvements, and the N-quaternization strategy is able to successfully achieve this goal with convenience. N-Quaternization of compound afforded Fluconazole bis-triazolium with superior bioactivity against \textit{Aspergillus fumigatus} (MIC = 16-32 \mu g/mL) to its precursor.
Experiments displayed that substituent $R_1$ had obvious influence on the yields of target compounds, and the various halobenzyl appended ones were especially favorable for the formation of target triazoliums with high yields more than 90%, while the large naphthalimide fragment highly limited this quaternization transformation due to its large blockade [282].

The transformation of triazoles through N-quaternization into the corresponding triazoliums has been an important pathway with convenient operations, mild conditions and good yields in the preparation of triazole derivatives with high water solubility.

4.5. C-Substitution of 1,2,4-Triazole Ring

The structural modification on the carbon atoms of the aromatic 1,2,4-triazole ring is another alternative access to produce triazole derivatives. However, the weak reactivity of C-substitution on triazole ring due to lower electronegativity in contrast with nitrogen atoms results in the few developments of C-substitution. Recently, researches have found that the metal catalyzed coupling reaction as a classical synthetic strategy can efficiently realize C-substitution on triazole ring, and much effort has been contributed to widen the application scope of C-C cross coupling reactions on aryl rings [283-289], especially on 1,2,4-triazole ring in organic chemistry. The reported C-substitution on 1,2,4-triazole ring is systematically involving cleavage of C-H and C-X bonds.

4.5.1. Cleavage of C-H Bonds

It has been an effective strategy by the use of coupling reaction to prepare aryl-aryl compounds in the presence of metal catalyst, and various multicomponent one-pot methods for triazoles syntheses using metal catalysts have been reported. The coupling reaction of methyl triazole 210 with iodobenzene could occur in 75-81% yields via one-pot manner to afford compound 213 with functionalized triazole core $\pi$ systems which was widely used in material and pharmaceutical chemistry owing to the good electron transporting and hole blocking abilities [291, 292]. It was worthy to notice that compound 212 could easily realize C-alkylation with paraformaldehyde in neutral conditions to prepare its hydroxymethylation derivative 214 in good yield of 81%. The hydroxymethyl triazole 214 could be further converted to the corresponding functional alkyl chloride 215a and aldehyde 215b (Scheme 93). Further researches displayed that the 3-methyl group in this compound could also undergo nucleophilic reaction with formaldehyde to give the corresponding diol when 3,4-dimethyl-1,2,4-triazole was employed as substrate [293].

4.5.2. Cleavage of C-X Bonds

The cleavage of C-X bonds of aromatic heterocycles is relatively easy in comparison with the corresponding C-H bonds. Recently, some effort has been directed towards the cleavage of halogenated 1,2,4-triazole derivatives to develop structurally novel triazole derivatives.
Current Developments in the Syntheses of 1,2,4-Triazole Compounds


Under the catalysis of CuI/Pd(PPh3)4, 3-carbamoyl triazole bromide 216 could react with a series of substituted phenylacetylenes in aqueous media via one-pot synthesis using microwave irradiation to give benzynyl triazole acyclonucleoside 217 (Scheme 94) [294]. Experimental results displayed that electron withdrawing groups such as CF3, Cl, Br, or CN at the 3- or 4-position on benzene ring resulted in low yields, which probably due to the reduced nucleophilicity and increased electrophilicity of the alkyne fragment. However, the electron donating n-butyl group at 4-position seemed to be specifically beneficial for this reaction which resulted in compound 217a with excellent yield up to 90% (Table 8).

Nucleoside analogues exhibit important antiviral and anticancer activities. A lot of effort has been engaged in developing various triazole nucleosides as potent antiviral and anticancer agents. However, the synthesis of N-aryl amino triazole nucleosides is a particular challenge due to the low reactivity of triazole ring, the multiple coordinating N- and O-atoms and the labile glycosidic bond. In the catalysis of unique mixed ligand system of Pd/Synphos/Xantphos, 5-bromotriazole ribonucleoside 218 successfully reacted with aniline to afford N-aryl aminotriazole nucleoside 219 (Scheme 95). Further evaluation of the reaction parameters demonstrated that the mole ratio of Synphos/Xantphos could highly affect this transformation. Compound 219 would be prepared in high yield of 92% when the mole ratio was 2/1. However, if Synphos or Xantphos was employed as the sole ligand, poor yields of 21-42% would be obtained [295].

Typical Suzuki coupling conditions were employed in the reaction of aryl boronic acid 220 with glycoside triazole 221 to generate aryl 1,2,4-triazole 222 as main product in moderate yield. In most cases, arylation took place predominantly at 5-position of triazole ring, though some 3-substituted and 3,5-disubstituted products were also observed as minor by-products. 1-Iodo-perfluorohexane was added to the dibrominated 1,2,4-triazole glycoside 221 by use of copper catalyzed coupling reaction to produce the 3-perfluoroalkyl-1,2,4-triazole 223 in yield of 37%, while 5-position was substituted by hydrogen. As part of the program directed toward the introduction of trifluoromethyl substituent to 5-position of triazole ring, compound 221 was treated with trimethyl(trifluoromethyl)silane. Unexpectedly, this reaction did not occur while an Ullman-type coupling product 224 was obtained. It was generally considered that 5-position of the 1,2,4-triazole ring was the most reactive site that the perfluoroalkyl group would be expected to attach here, instead, the competing hydrodebromination at 5-position proceeded at a faster rate than the coupling reaction, so the perfluoroalkyl group appeared at the 3-position (Scheme 96) [258].

Table 8. Effects of Substituents on the Formation of Compounds 217a-e

<table>
<thead>
<tr>
<th>Compound 217</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
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</tbody>
</table>

Scheme 94.

Scheme 95.
Dendrimers as monodisperse and well-defined macromolecules are prepared by divergent or convergent iterative procedures with different sizes and generations. The unique properties associating with the perfectly branched dendritic architecture are highly appreciated and have been widely used in various aspects, but their syntheses are crucially difficult. In the presence of potassium carbonate, the disubstituted 1,2,4-triazole reacted with the substituted phenol in a refluxing mixture of DMF and toluene (V/V = 2/1) to efficiently produce 1,2,4-triazole dendrimer in 80% yield.

Compound may be used as novel rigid homogeneous dendritic catalyst and organic light emitting diode (Scheme 97) [296].

Very recently, C-substitution of aromatic ring through cleavage of C-H or C-X bonds has attracted substantial interest and becomes one of the most straightforward and useful methods to prepare innovative compounds especially aryl triazole derivatives with environmentally green and benign advantages [286].

5. STRUCTURAL MODIFICATIONS IN SIDE CHAINS OF 1,2,4-TRIAZOLES

Structural modifications in side chains of 1,2,4-triazole ring as another practical method are prevalently used to construct 1,2,4-triazole derivatives. Due to the high reactivity of amino and thiol groups in 1,2,4-triazoles, they easily proceed diverse reactions to modify the side chains of 1,2,4-triazole ring to construct novel heterocycles [39,297,298]. According to the modified functional groups, this type of structural modifications principally included the following aspects: (1) Modification of Thiol Groups; (2) Modification of Amino Groups; (3) Modification of both Thiol and Amino Groups; (4) Modification of Active Methylene Groups; (5) Modification of Other Functional Groups.

5.1. Modification of Thiol Groups

The presence of the sulfur moiety as an electron rich center is able to improve lipophilicity and modulate electron density of the triazole ring, thereby influencing its transmembrane diffusion ability to the anticipant targets, as well as its interaction with hydrogen bond donors of the organism. Naturally, the introduction of sulfur moiety attracts special interest in the design of new drugs. Triazole thiols are in tautomeric equilibrium with triazole thiiones, and both of them have two resonance forms (I₁ and I₂) in the presence of base. Researches have revealed that thermodynamic products triazole thiiones are obtained as major products at high temperature (80 °C) via the formation of compound I₁, while the thiol group is generally converted into thioether at room temperature (Fig. 4) [126,299]. Recently, modification of thiol group of 1,2,4-triazole derivatives has been becoming one of the leading directions to search for biologically active compounds.
It is well known that thiol groups in triazole thiols have high reactivity, and they can easily react with a series of halides in the presence of base. The reaction of 3,4-disubstituted 5-thiol-1,2,4-triazole which was provided by the intramolecular cyclization of thiosemicarbazides in alkaline medium and subsequent acidification with acetic acid, with benzyl or isoamyl chlorides under basic condition could afford S-substituted triazole in 50-95% yields (Scheme 98) [300]. Researches demonstrated that substituents on benzene ring had large influence on this transformation. The substitution pattern of compound \( \text{228c} \) gave the highest yield of 95%, while compound \( \text{228a} \) provided the lowest one (50%) (Table 9).

The classical preparative methods for thioether triazoles normally proceed in the presence of strong base under refluxing condition. However, this type of reactions requires long refluxing time and the yields are usually very low. Therefore, metal catalyzed reactions are employed because of mild reaction conditions and high yields. In the presence of indium trichloride, triazole thiol could react with a series of halides to give potential fungicidal thioether triazole in excellent yields (Scheme 99) [301]. Several catalysts like InCl\(_3\), AlCl\(_3\), ZnCl\(_2\), PdCl\(_2\), CuI and metal Cu were screened to investigate their effects on this reaction. The results showed that the best catalytic activity was achieved when InCl\(_3\) was used to promote the reaction and the yields were up to 84-91%.

The incorporation of ferrocene fragments into molecules particularly heterocyclic ring often give hybrids with unexpected biological activity, and which has been recognized as an attractive way to prepare novel molecules. The conjunction of triazole thiol with ferrocene containing α-halo-substituted ketone in the presence of sodium hydride and potassium iodide successfully produced compound which possessed unique membrane permeation properties and anomalous metabolism (Scheme 100). The experimental results manifested that substituents on benzene ring influenced the product yields to a large extent, and the electron donating group 4-CH\(_3\)OPh was more favorable for the thio etherification than the electron withdrawing 4-NO\(_2\) one, unexpectedly, 3-Br substituent was also helpful for the progress of this reaction (Table 10) [302].
As is reported, triazole thiol can react with chlorine gas to conveniently and efficiently afford sulfonyl derivatives with interesting properties. Reaction of 3,4,5-trisubstituted triazole thiol with chlorine gas conveniently produced sulfonyl triazole, and the latter subsequently reacted with amine to provide compound with superior antimicrobial activity to its precursor (Scheme 101) [303]. This strategy presents an important way for the preparation of sulfonyl triazole derivatives and also extends the development space of novel sulfanilamide compounds.

In addition, thiol group in 3-thiol-1,2,4-triazole could be removed by hydrogen peroxide in presence of acetic acid via mild oxidation to yield the corresponding 3-unsubstituted triazole in 82-86% yields. Experiments showed that compound readily underwent hydroxymethylation at triazole ring under neutral condition to generate triazole alcohols and subsequent oxidation with manganese dioxide to afford corresponding triazole aldehydes in good yields ranging from 71% to 94% (Scheme 102) [293].

5.2. Modification of Amino Groups

Amino 1,2,4-triazoles as important reactants with high reactivity have large potential applications in synthetic chemistry. Generally, they easily undergo condensation with unsaturated compounds such as aldehydes, ketones, thiocyanate and isothiocyanate esters to construct intriguing molecules with spacious application in various fields like organic, medicinal and material chemistry.

A lot of researches have demonstrated that thiourea fragments play unusual contribution to bioactivity and are frequently introduced into drug molecules. Experiment results displayed that the condensation of 3-amino 1,2,4-triazole with aryl isothiocyanates efficiently afforded thiourea triazole in yields of 71-93%, while alkyl isothiocyanates were employed as materials, the N-2 atom of 1,2,4-triazole ring might take part in the reaction to give product with unsubstituted amino group in excellent yields ranging from 71% to 94% (Scheme 102) [293].

Thiosemicarbazones with thiouile-thiol tautomers are a very promising class of compounds showing a broad spectrum of therapeutic properties. Recent researches showed that the hybrids of thiosemicarbazone with triazoles could effectively inhibit the growth of Entamoeba histolytica. The condensation of 4-amino-5-phenyl-4H-1,2,4-triazole-3-thiol with various substituted aromatic aldehydes in the presence of hydrochloric acid afforded triazole in good yields (62-70%) (Scheme 104). Further studies demonstrated that substituents on benzene ring such as methyl, methoxy or nitro groups gave little influence on this transformation, but they showed obvious effect on inhibiting the growth of Entamoeba histolytica [305]. In the same conditions, coumarin triazoles were prepared in yields of 74-76%, and the produced compounds were further transformed into Co(II), Ni(II), and Cu(II) complexes with good DNA cleavage activity [306].

Amino triazole can also easily react with sulfonyl group to afford special triazole derivatives. Reaction of amino 1,2,4-triazole with compound through deprotonation with lithium bis(trimethylsilyl)amide (LiN(TMS)_2) successfully afforded triazole derivative in yield of 73% and then deprotection of the side chain via sequential treatment by hydrogen chloride and sodium.

<table>
<thead>
<tr>
<th>Compound 233</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
<th>e</th>
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<tbody>
<tr>
<td>R</td>
<td>H</td>
<td>4-CH₃</td>
<td>4-OCH₃</td>
<td>4-NO₂</td>
<td>3-Br</td>
</tr>
<tr>
<td>Yield (%)</td>
<td>57</td>
<td>73</td>
<td>87</td>
<td>24</td>
<td>80</td>
</tr>
</tbody>
</table>

Table 10. Effects of Substituents on the Formation of Compounds 233a-e
hydroxide provided a novel potent and efficacious 3-hydroxy-3-methylglutaryl coenzyme-A reductase (HMGR) inhibitor, which might be used in treating hypercholesterolemia and dyslipidemia with potentially excellent safety profile (Scheme 105) [307].

By the use of microwave irradiation, the one-pot reaction of salicylic aldehyde 244, 3-amino 1,2,4-triazole and acetone in ethan- 

ol at 170 °C gave triazole derivative 245 in moderate yield (47%). If the reaction was performed at 40 °C in methanol, the diol product 246 would be obtained as main product in 60% yield. The structures confirmed by single crystal X-ray diffraction clearly showed that the condensation of 3-amino 1,2,4-triazole with aldehyde occurred in the exocyclic amino group not on the endocyclic nitrogen of triazole ring (Scheme 106) [308].

An increasing interest has recently been focusing on heterocyclic macrocycles because of their large potentiality as medicinal drugs like magnetic resonance imaging agents Magnevist and MultiHance, anticancer agents cyclodextrin- and porphyrin-based supermolecules, etc. [30,31]. Multinitrogen triazoles with strong coordination ability have been of great importance in the development of macrocyclic complexes. The reaction of bis(2-formylyphenyl)hexane 247 with 3-substituted-4-amino-5-hydrazino-1,2,4-triazole 248 in 1:1 molar proportion by adding a few drops of hydrochloric acid have successfully provided macrocyclic Schiff base triazole 249 in yields ranging from 55% to 60%, and its complexes with metal Co(II), Ni(II) and Cu(II) ions exhibited magnetic properties and among them Co(II) complexes had highest magnetic moments (4.70-4.94 BM) than the other ones (Scheme 107) [309].

In addition, the amino group on triazole ring could also be transformed into diazonium salts, nitro and other derivatives [173,310-313]. These studies may lead to the rational design of even more effective and stable molecules with potential valuable application in various aspects.

5.3. Modification of Both Thiol and Amino Groups

The thiol and amino substituted triazoles as one of the most important molecular fragments to develop bioactive compounds are widely employed to construct fused heterocycles [314]. In sulphuric acid medium, the N-alkylation of amino group in compound 250 with aromatic aldehydes and thiglycolic acid gave triazole intermediate J1, and then was dehydrated and converted into thiadiazole 252 affording corresponding compound 253 in yields of 66-70% and then the products were converted into crown ether 254 with remarkable host-guest complexation characteristics and antibacterial activities (Scheme 109). As an extension of this study, 1,3,4-thiadiazole containing crown macrocycles were also successfully prepared in moderate yields (55-80%) [316].

5.4. Modification of Active Methylene Groups

It is well known that α-hydrogens in active methylene groups which are activated by electron withdrawing groups can easily be
modified to provide special structures containing chalcone fragments. These chalcone structures have typical acyclic conjugated backbone, desirable intramolecular charge transfer and unusual fluorescence emission properties as well as easy structural modification by various functional groups. It is of great interest to incorporate these special fragments into 1,2,4-triazole to give the new skeleton with broad bioactive spectrum [317]. The chalcone containing triazole 256 was prepared via aldol condensation of compound 255 with benzaldehyde in toluene under the cocatalysis of both glacial acetic acid and piperidine. The key intermediate ethanone in 1,2,4-triazole 255 was efficiently obtained in excellent yield of 93% starting from commercially available m-difluorobenzene.
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through Friedel-Crafts acylation and then N-alkylation with 1,2,4-triazole in one-pot synthesis (Scheme 110). Further observations indicated that the amount of piperidine was quite an important factor in the formation of amino chalcone hybrids [318, 319]. In addition, compound 255 could be brominated by bromine to give antimicrobial 2-bromo-2-(5-bromo-1H-1,2,4-triazol-1-yl)-1-(2,4-difluorophenyl)ethanone in the presence of acetic acid [320].

As presented in (Scheme 110), mixture of triazole compound 257 and equimolar aromatic aldehydes produced two compounds with architectonic E-chalcone-triazole 258a (38-55%) and its isomer Z-one 258b (8-10%) in the catalysis of piperidine and glacial acetic acid. Single crystals of target compounds were successfully cultivated and the structures were measured by X-ray diffraction (Scheme 111). It could be seen from the stereoscopic configuration that the Z type compound was a forceps-shaped structure in which the distance between molecules was far and the intermolecular interaction was weak due to the influence of steric effects. However, the E type one could efficiently generate self-assembly via intermolecular π-π stacking interactions. It was generally considered that this transformation would be highly affected by the blockade of the substituents, and the large anthracene ring was unfavorable for this reaction with yields low to 38% and 8% for E- and Z- types respectively [321-324].

Recently, metal complex inhibitors have extensively been used to treat human immunodeficiency virus (HIV) infections, the emergence of serious toxicity and drug resistant strains has highly promoted the need for new inhibitors that can resolve these issues.

Reaction of ester containing tetrahydropyranyl 1,2,4-triazole 259 with compound 260 successfully produced α,β-unsaturated carbonyl triazole 261 with potent anti-HIV activity using a low cost and reliable synthetic procedure (Scheme 112) [325].

Additionally, chloromethyl triazoles display strong reactivity for that the electron withdrawing aromatic triazole ring largely decreases electron density of C-Cl bond. In the presence of potassium carbonate, dichloromethyl triazole 262 smoothly reacted via etherification with 2 equivalent salicylaldehyde to give chemosensor precursor 263, and the latter as semirigid ligand containing lone electron pairs on nitrogen atom, could easily coordinate with copper(II) to construct highly sensitive and selective “off-on” chemosensor chelates (Scheme 113) [326]. It is anticipated that this synthetic reaction may be served for the developments of new chemosensors for other transition metal ions, and which will significantly promote the investigation of the effects on cations in biological systems.

5.5. Modification of Other Functional Groups

Except for the above mentioned structural modifications of functional groups, some other groups such as hydroxyl, azide ones and so on in side chains of triazole ring can also be converted to provide various intriguing triazole derivatives with potential applications.

Etherification of 1-phenyl-1,2,4-triazole-3-ol 90 with a variety of alkyl bromides and benzyl halides afforded alkoxy 1,2,4-triazole 264 and halobenzyloxy derivative 265 in yields ranging from 56%

Scheme 113.

Scheme 114.

to 89%, and then they were further treated by hydrochloric acid (4 mol/L) in ethyl ether to produce their corresponding hydrochlorides in high yields (81% to 88%) which gave significantly improved antimicrobial activities in comparison with their precursor triazoles (Scheme 114) [115]. It should be noted that the ratio of reactants, solvents, reaction time, amount of catalyst as well as the addition rate of sulfuric acid exerted important influences on the yields of target triazoles, and experiments confirmed that the presence of weak base such as potassium carbonate in acetonitrile at 70-75 °C was favorable for this O-alkylation reaction.

Click chemistry is now being extensively studied, and is easy to perform quickly and reliably by joining small units together. Click reaction as one of the most popular reactions in click chemistry is defined as Cu(I) catalyzed 1,3-dipolar cycloaddition of azide moiety and alkyne to build 1,2,3-triazole ring. This efficient coupling reaction is of great potential to build multifunctional molecules due to its high regioselectivity, quantitative yields and mild reaction conditions without by-products [206,207,327]. Recently, double triazole compounds have been attracting considerable interest due to their unique structures and properties, among which Fluconazole is the representative one with powerful antifungal activity, and also 1,2,3-triazoles with excellent properties have attracted much attention. Therefore, the interest in developing conjugated molecules of both 1,2,4- and 1,2,3-triazole rings was highly increased. The click reaction of azido-1,2,4-triazole 266 with phenylacetylene 267 under mild copper catalyzed conditions favorably produced 1,2,4-triazole derivative 270, and subsequent transformation gave amide ditriazoles as novel antiviral candidates against Tobacco Mosaic Virus (Scheme 115) [328].

Selenium microelement is introduced into triazole skeletons to produce compounds with good bioactivity and high safety. Herbicide precursor arylselenonyl-1H-1,2,4-triazole 270 was prepared by the reaction of diazonium salt, which was obtained by the transformation of arylamine, with compound 269, and target compounds were further oxidated by oxone and subsequently N-acylated with diethylcarbamoyl chloride to produce diethylamide triazole with herbicidal activity. In order to ensure the process of the reaction, the pH values must be strictly kept at 12 (Scheme 116) [329]. This transformation is highly affected by the temperature, pH and complicated operations, and only exhibits narrow application scope, but it can provide rare triazole selenium herbicides and much effort should be dedicated to this strategy to optimize the harsh reaction conditions.

Additionally, the modification of functional groups which are far from triazole ring has been reported vastly due to the easily coupling reactions, and numerous 1,2,4-triazole-based supramolecular aggregates have been prepared with special properties and biological activities, and display a wide range of potential application as cation and anion artificial receptors [330-335], luminescent [336-340] and magnetic [341-344] materials as well as medicinal agents [3,30-32].

6. CONCLUSION

The above mentions have clearly demonstrated that the highly efficient syntheses of 1,2,4-triazole derivatives have been fast developed, and a great amount of effort has been directed towards synthetic strategies and lots of excellent achievements have been acquired. Particularly excited is that an increasingly number of new synthetic technologies have been developed to prepare triazole
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compounds in actively ongoing researches. All these clearly pointed out that preparation of triazole containing compounds will provide an infinite space for synthetic chemists. It is undoubtedly believed that the researches and developments of synthetic methods of 1,2,4-triazoles will still be one of the most active areas in a long time. From current researches, the active topics in syntheses of 1,2,4-triazole derivatives in near future might mainly include the following aspects:

(1) Increasing effort will continuously contribute to cyclizations to form 1,2,4-triazole derivatives.

Cyclizations of hydrazines and their derivatives as starting materials will still be one of the most important synthetic routes to access novel 1,2,4-triazoles with variation of substituents. More and more work will extend to commercially available non-hydrazone compounds to construct 1,2,4-triazoles with completely new chemical structures. Particularly, one-pot synthetic methods to produce triazoles will become important direction.

(2) The substitutions of triazole ring will continuously be an unusually prevalent topic for the preparation of 1,2,4-triazole-based compounds. Especially, with the rapid progress of C-H synthetic methodology, the functionalization of triazole C-H bonds by electrophilic attack of metal ions might become active area to prepare novel triazole compounds.

(3) Transformations of heterocycles might still be an important strategy to access novel 1,2,4-triazoles with special structures. However, this type of synthetic pathway is highly limited due to the difficult preparation of precursor heterocycles.

(4) Structural modifications in side chains of triazole ring by a variety of biologically important structural fragments including other azole rings [7] like imidazole [81], tetrazole [345], oxazole [178], benzimidazole [129,130] etc. will still be a highly prevalent pathway to access 1,2,4-triazole derivatives with novel chemical structures and variable properties. In particular, the moieties with unstable and sensitive properties can be easily improved to generate more stable triazoles.

Clearly, with increasing effort towards the synthesis of 1,2,4-triazole derivatives, more and more synthetic technologies with mild conditions, convenient operations, high efficiencies and so on will be contributed to the preparation of various sorts and varieties of 1,2,4-triazoles with diverse potential applications in chemical, medicinal, agricultural, material sciences and so on.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

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REFERENCES

[15] Naik, A.D.; Durtu, M.M.; Railliet, A.P.; Marchand-Brynaert, J.; Garcia, Y. Coordination polymers and metal organic frameworks derived from 1,2,4-triazole amino acid linkers: Polymers (Basel, Switzerland), 2011, 3, 1750-1775.


[42] Bhagavathula, S.D. Process for preparation of 1,2,4-triazole with minimum formation of 4-amino-1,2,4-triazole. IN Patent IN2009,M01331 (A), December 2010.


The development and synthesis of 1,2,4-triazole compounds have been extensively studied due to their unique chemical and biological properties. This review focuses on the latest advancements in the syntheses of 1,2,4-triazole compounds, highlighting various methodologies and the applications of these compounds in different fields. The review covers a wide range of topics, including the synthesis of 1,2,4-triazole derivatives, their biological activities, and their potential applications in medicinal chemistry.

### Synthesis of 1,2,4-triazole Compounds

1. **One-pot Synthesis:** A one-pot synthesis of 1,2,4-triazole derivatives has been reported using a convenient reagent. This method has the advantage of being simple and efficient, allowing for the rapid preparation of a variety of 1,2,4-triazole derivatives.

2. **Antimicrobial Activity:** Several 1,2,4-triazole derivatives have shown promising antimicrobial activity against various bacterial strains. These compounds have potential for use as new antimicrobial agents.

3. **Synthesis of Triazole Derivatives:** The synthesis of triazole derivatives using 2-(4-halophenyl)-1,2,4-triazole-3-yl-disulfane has been reported. The reaction involves the cleavage of the S-S bond in a Co(II) complex membered chelate ring complex of Mn(II) derived from bis(5-phenyl-2-1H-1,2,4-triazole)-3-yl-disulfane and the formation of a Co(II) complex.

4. **Oxytocin Antagonists:** Triazole oxytocin antagonists have been identified as a new class of oxytocin receptor antagonists. These compounds have potential for use in the treatment of uterine fibroids and other uterine disorders.

5. **Organometallic Compounds:** The synthesis and characterization of organometallic compounds containing 1,2,4-triazole moieties have been reported. These compounds have potential for use as new antimicrobial and antitumor agents.

6. **Antitumor Agents:** Several 1,2,4-triazole derivatives have shown promising antitumor activity against various cancer cell lines. These compounds have potential for use as new antitumor agents.

7. **Antiviral Activity:** Several 1,2,4-triazole derivatives have shown promising antiviral activity against various viral strains. These compounds have potential for use as new antiviral agents.

8. **Antifungal Activity:** Several 1,2,4-triazole derivatives have shown promising antifungal activity against various fungal strains. These compounds have potential for use as new antifungal agents.

9. **Antioxidant Activity:** Several 1,2,4-triazole derivatives have shown promising antioxidant activity. These compounds have potential for use as new antioxidant agents.

10. **Anticonvulsant Activity:** Several 1,2,4-triazole derivatives have shown promising anticonvulsant activity. These compounds have potential for use as new anticonvulsant agents.

### Applications of 1,2,4-triazole Compounds

1. **Medicinal Chemistry:** The 1,2,4-triazole scaffold is widely used in the design and synthesis of novel medicinal agents. These compounds have potential for use as new drugs.

2. **Agricultural Chemistry:** Several 1,2,4-triazole derivatives have shown promising activity against various plant pathogenic fungi. These compounds have potential for use as new fungicides.

3. **Environmental Chemistry:** Several 1,2,4-triazole derivatives have shown promising activity against various environmental pollutants. These compounds have potential for use as new detoxification agents.

4. **Materials Science:** Several 1,2,4-triazole derivatives have shown promising activity as new materials for various applications. These compounds have potential for use as new materials.

The continued exploration of the 1,2,4-triazole scaffold in various fields will undoubtedly lead to the discovery of new and innovative applications of these compounds.
Hou, Y.P.; Sun, J.; Pang, Z.H.; Lv, P.C.; Li, D.D.; Yan, L.; Zhang, H.J.; Meng, J.P.; Geng, R.X.; Zhou, C.H.; Gan, L.L. Advances in the research of Ku
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1,2,4-triazole)-based energetic salts: synthesis and promising properties of a new family of high-density insensitive materials. J. Am. Chem. Soc., 2010, 132, 11904-11905.


[181] Li, Z.Z.; Gu, Z.; Yin, K.; Zhang, R.; Deng, Q.; Xiang, J.N. Synthesis of disubstituted-(NH)-1,2,4-triazole derivatives from 3,6-diaryl-1,2,4,5-tetrazines.

[182] Zhou, C.H.; Mi, J.L. Preparation of Fluotrimazole ether derivatives as antimi-


[184] Zhou, C.H.; Fang, B.; Gan, L.L. Benzyl chloride tertiary amine double azole synthesis and SAR of newly synthesized 1,2,4-triazoles.


[188] Francis, G.; Rémi, G.; Cédric, L.; Fabrice, P.; Carine, P.; Marc, L.B.; Patrice, L.P. Synthesis and structure-activity relationships of 2-phenyl-1-[(pyridinyl 1,2,4-triazole 4-yl) methylene]-4-(2,6-dimethylphenyl)azepinyl 4-fluoro-3-hydroxy-4(1H)-quinolinones as novel glycinetransporter inhibitors.

[189] Zhou, C.H.; Fang, B.; Gan, L.L. Benzyl chloride tertiary amine double azole synthesis and SAR of newly synthesized 1,2,4-triazoles.


[194] Zhou, C.H.; Fang, B.; Gan, L.L. Benzyl chloride tertiary amine double azole synthesis and SAR of newly synthesized 1,2,4-triazoles.

[195] Zhou, C.H.; Fang, B.; Gan, L.L. Benzyl chloride tertiary amine double azole synthesis and SAR of newly synthesized 1,2,4-triazoles.

[196] Zhou, C.H.; Fang, B.; Gan, L.L. Benzyl chloride tertiary amine double azole synthesis and SAR of newly synthesized 1,2,4-triazoles.

[197] Haddadin, M.J.; Zadeh, E.H.G. A novel method for the synthesis of 3,5-disubstituted-(NH)-1,2,4-triazoles from 3,6-dihydropyrano[1,2,4]triazines. Tetra-


[200] Zhou, C.H.; Wu, J.; Jin, S.; Li, M.; Li, J.; Zhang, F.F.; Fang, B. 1,2,4-triazoles com-


[203] Zhou, C.H.; Fang, B.; Gan, L.L. Benzyl chloride tertiary amine double azole synthesis and SAR of newly synthesized 1,2,4-triazoles.

[204] Zhou, C.H.; Fang, B.; Gan, L.L. Benzyl chloride tertiary amine double azole synthesis and SAR of newly synthesized 1,2,4-triazoles.

Luo, Y.; Lu, Y.H.; Zhou, C.H.; Wu, J.; Geng, R.X.; Zhang, Y.Y. Bistriazolone, bistriadimenol compounds with antimi...)

Zhang, J.; Yu, C.W.; Qian, S.Y.; Lu, G.; Chen, J.L. A selective fluorescent chemosensor with 1,2,4-triazole as subunit for Cu(II) and its application in imaging Cu(II) in living cells. Dyes Pigments, 2012, 92, 1370-1375.

Ambiard, F.; Cho, J.H.; Schnazzi, R.F. Cu(I)-Catalyzed huisgen azide alkyl 1,3-dipolar cycloaddition reaction in nucleoside, nucleotide, and oligonucleotide chemistry. Chem. Rev., 2009, 109, 4207-4220.


