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Exploring the versatility of heterocyclic compounds containing nitrogen atoms (triazoles): a comprehensive review

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Heterocyclic compounds are cyclic compounds with atoms from at least two different elements in their ring. They play vital roles in regulating biochemical processes in living systems that involve hormones, enzymes, and genetic materials. Among the heterocyclic compounds, triazoles have a fascinating structure that comprises three nitrogen atoms and two carbon atoms. Generally, they are divided into two type of isomers, namely, 1,2,3-triazoles and 1,2,4-triazoles, representing a diverse and essential class of molecules in organic chemistry. Their immense applications in pharmaceutical chemistry and agrochemistry make them vital for humankind. This review is a perfect blend for the researchers and practitioners seeking to explore the versatility, functional diversity, and synthetic methodology of 1,2,3-triazoles and 1,2,4-triazoles from various carbon and nitrogen sources.

1 Introduction

Nitrogen-containing heterocyclic compounds are abundant in nature and play significant roles in many biochemical substances such as vitamins, nucleic acids, medicines, dyes, and agrochemicals. They are well-known in the fields of organic and medicinal chemistry due to their immense applications, which are growing quickly.[1–13] In this connection, Bladin developed a five-membered cyclic ring containing three nitrogen atoms, known as a triazole, with the molecular formula of $C_2H_3N_3$.[14] Triazoles exists in two different isomeric forms, 1,2,3-triazoles and 1,2,4-triazoles, which are also known as pyrrodiazole.[15,16] The isomeric forms of 1,2,3-triazoles and 1,2,4-triazoles, as well as benzotriazoles, are shown in Fig. 1. Generally, triazoles exist as monocyclic, benzotriazoles, or in their salt form.[17] Monocyclic triazoles and benzotriazoles show high reactivity towards enzymatic degradation, hydrolysis, and oxidation.[18]

Triazole chemistry was gradually developed and attracted much attention from researchers owing to their emerging facile, convenient, and modern synthetic routes along with their diverse interactions with biological systems.[19]

Generally, triazole derivatives have a wide range of biological activities,[20–25] like antifungal (Fig. 2),[26–28] herbicidal (Fig. 3),[29–31] and fungicidal (Fig. 4) properties.[32,33] In addition to these

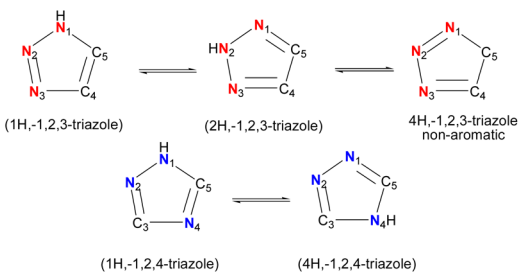

Fig. 1 Isomeric structures of 1,2,3- and 1,2,4-triazoles.

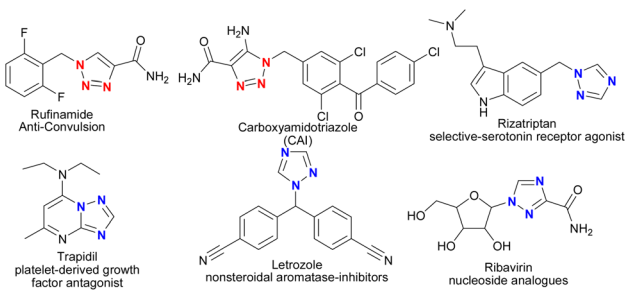

Fig. 2 Triazole-based antifungal compounds.

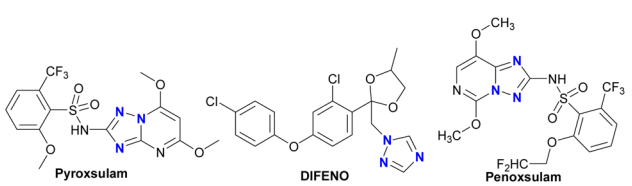

Fig. 3 Herbicides containing a triazole moiety.

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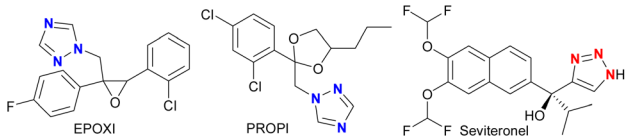


Fig. 4 Some examples of fungicide molecules.

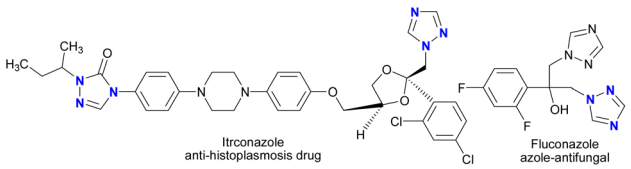


Fig. 5 First-generation triazoles.

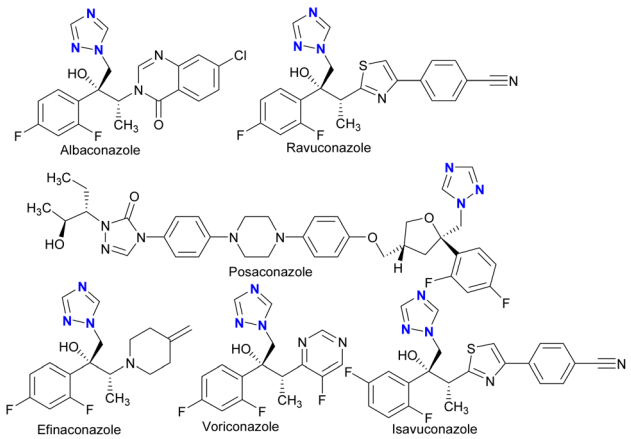
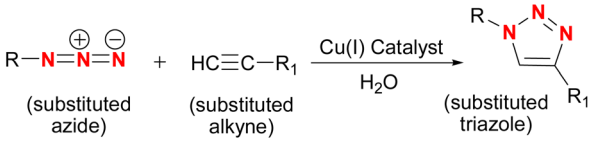


Fig. 6 Second-generation triazoles.

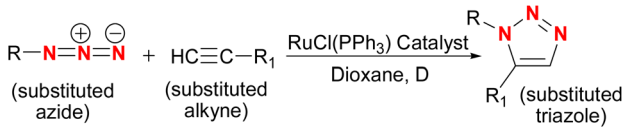
applications, it is also known that triazole-based molecules have excellent anti-HIV, anti-inflammatory, anti-cancer, anti-bacterial, anti-viral, anti-microbial, anti-depressant, and anti-oxidant properties.[34–38] Triazoles have been classified into two generations (Fig. 5 and 6) based on their antifungal impacts.[39]

2 Mechanistic studies of triazoles

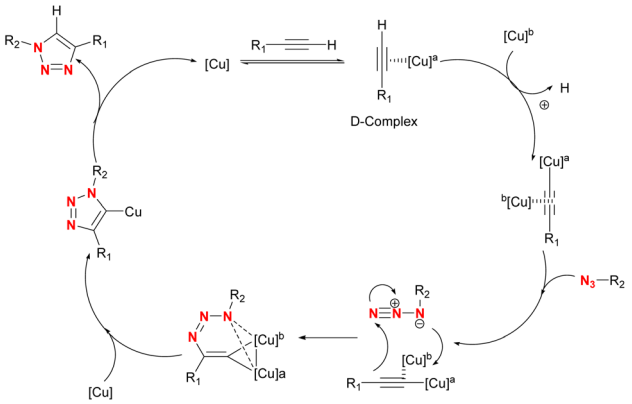
Owing to the biological properties of triazoles, researchers started to work on the development of various synthetic methods for the synthesis of triazole derivatives. In this regard, initially Rolf Huisgen and co-workers proposed the copper-catalyzed azide–alkyne cycloaddition (CuAAC) reaction (Scheme 1),[40] which was later developed by Meldal and



Scheme 1 Copper-catalyzed azide alkyne cycloaddition (CuAAC).



Scheme 2 Ruthenium-catalyzed azide alkyne cycloaddition (RuAAC).



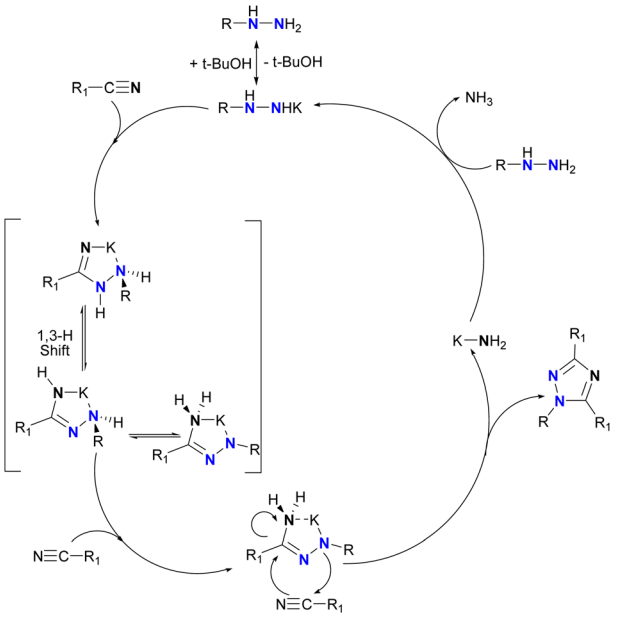
Scheme 3 Mechanism of the formation of 1,2,3-triazole by Huisgen 1,3-dipolar cycloaddition.

Sharpless.[41–45] The azide–alkyne cycloaddition reaction has further developed with ruthenium metal instead of copper and named ruthenium-catalyzed azide–alkyne cycloaddition (RuAAC) (Scheme 2).[46–48]

This method was reported at the start of the 20th century, but its specific mechanism was already described by Huisgen *et al.* in 1967. The general mechanism for the synthesis of 1,2,3-triazole is shown in Scheme 3. The reaction proceeds *via* a concerted 1,3-dipolar cycloaddition between an organic azide and an alkyne, forming a five-membered triazole ring in a single step. The cycloaddition is thermally allowed and is regio-isomeric, yielding both 1,4- and 1,5-disubstituted triazoles depending on the reaction conditions and dipolarophile orientations.[49–51]

On the other hand, the 1,2,4-triazole core is most commonly constructed by cyclization reactions involving hydrazines (or hydrazide/hydrazone intermediates) and amine- or nitrile-based precursors. The general mechanism for the synthesis of 1,2,4-triazole is shown in Scheme 4. The reaction generally proceeds through nucleophilic attack of the hydrazine nitrogen on the carbonyl or imine carbon, forming a hydrazone or amidrazone intermediate. Subsequent intramolecular cyclization followed by dehydration or oxidative aromatization leads to the formation of the 1,2,4-triazole ring system.[52–56]

Triazoles possess exceptional mechanistic and electronic features. Their five-membered, nitrogen-rich ring is aromatic and exhibits strong π-delocalization and tautomeric flexibility, leading to remarkable thermal and metabolic stability. These characteristics make triazoles potent pharmacophoric linkers, mimicking amide or peptide bonds and enhancing the bioavailability of molecules. Moreover, their lone-pair-bearing nitrogen atoms enable co-ordination to transition metals and



Scheme 4 Mechanism of the formation 1,2,4-triazole from hydrazines and cyanides.

facile conversion into mesoionic triazolylidene carbenes, which serve as powerful σ-donor ligands in catalysis.[57–61]

2.1 Computational, mechanistic, and green chemistry insights

In recent years, the integration of computational and mechanistic studies has provided deeper insights into the reactivity and selectivity of triazole-forming reactions. Density functional theory (DFT) calculations and artificial force-induced reaction (AFIR) methods have elucidated key transition states and intermediates, thereby rationalizing the regioselectivity and catalytic efficiency in copper-catalyzed azide–alkyne cycloaddition (CuAAC) reactions. Furthermore, mechanistic understanding has guided the development of green chemistry approaches such as sustainable, metal-free, reduced reaction time and energy consumption and solvent-free protocols. The adoption of green solvents, ionic liquids, and microwave-assisted conditions not only enhances the reaction efficiency but also minimizes its environmental impact. These advancements collectively bridge fundamental mechanistic understanding with practical synthetic sustainability in triazole chemistry. Also, these studies reveal that electronic effects govern the regioselectivity, reactivity, and catalytic performances of triazoles.[62–69]

2.2 Novelty and significance

This review presents unified and comparative insight into the synthesis of 1,2,3- and 1,2,4-triazoles, correlating their mechanistic pathways, catalytic systems, and sustainable advancements. Previous reviews predominantly focused on isolated aspects such as structural diversity and classical routes,[70] pharmacophoric and CuAAC-based click methodologies,[71] functionalization chemistry,[72] and condensation strategies for 1,2,4-triazoles.[73] Others emphasized biological and medicinal relevance rather than synthetic innovation.[74] The present work bridges these gaps by critically evaluating both isomers across metal-catalyzed, metal-free, and nanoparticle systems, highlighting their microwave-assisted synthesis. Furthermore, this review establishes a comprehensive, sustainability-oriented synthesis platform that extends beyond prior triazole literature.

3 Synthetic approaches for triazoles

The wide range of applications, low molecular toxicity, highly efficient analogues, and promising research directions of various triazoles and their derivatives have prompted researchers to design many synthetic and modern strategies. The availability of reagents and simplicity of their synthetic procedures justified this fact.

3.1 Synthesis of 1,2,3-triazole analogues

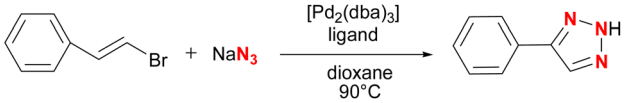
In organic chemistry, the 1,2,3-triazole group is the most important and promising moiety and significant functional group of aromatic compounds.

3.1.1 Using metal source as a catalyst. Similar to the preparation of vinyl azides by the coupling of an azide with alkenyl halides, Jos Barluenga and co-workers developed 1*H*-1,2,3-triazoles serendipitously. This unexpected result represents a novel method for the preparation of 1*H*-1,2,3-triazoles and new reactivity for palladium (Pd^0) catalysts. In this method, triazoles can be synthesised *via* the reaction between alkenyl halides with azide anions under palladium catalyst proceeding *via* a C–N cross coupling reaction (Scheme 5).[75]

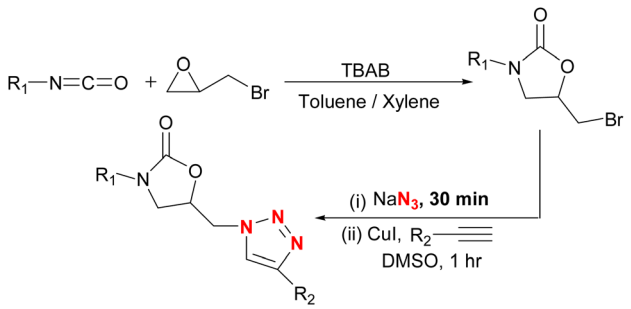
Demaray and co-workers prepared substituted triazole-oxazolidinones using a bromide catalyst *via* three-component Huisgen cycloaddition between aryl isocyanates and epibromohydrin. The prepared derivatives of the triazole-oxazolidinones act as good antibacterial agents against *Mycobacterium smegmatis* ATCC 14468 (Scheme 6).[76]

A simple and convenient method was developed for the synthesis of substituted 1,2,3-triazoles from stable and readily accessible 1-iodoalkynes and organic azides. The reaction is mediated *via* copper-catalyzed annulation. This is because 1-iododacetylenes exhibit exceptional reactivity in the presence of a copper catalyst. Also, the catalysis is affected by copper(I) iodide in the presence of an amine ligand. Copper(I) iodide–triethylamine is essential as no reaction was observed when TEA was omitted for the formation substituted 1,2,3-triazole derivatives (Scheme 7).[77]

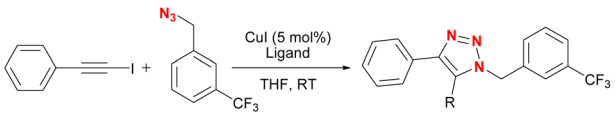
The silver(I) catalyst-mediated synthesis of 1,2,3-triazoles using azides and terminal alkynes was reported in 2012 by



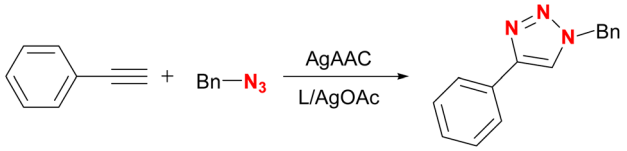
Scheme 5 Synthesis of 1,2,3-triazoles from alkenyl halides and azide anions.



Scheme 6 Synthesis of 1,2,3-triazoles *via* three-component cycloadditions.



Scheme 7 Synthesis of 1,2,3-triazoles from iodoalkynes and azides.

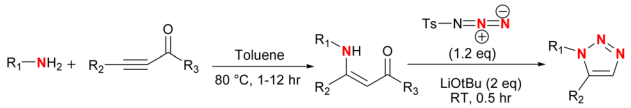


Scheme 8 Silver catalyst-mediated synthesis of 1,2,3-triazoles.

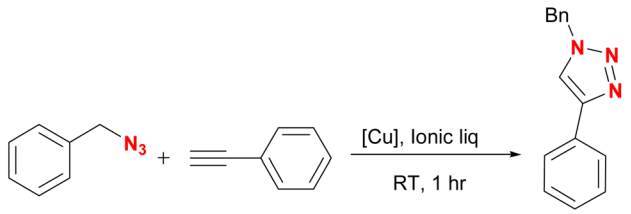
James McNulty and Kunal Keskar. The silver(I) catalyst used in this method is a highly efficient, chemically stable and well-defined homogenous catalyst. This reaction proceeds through the cycloaddition of azides to terminal alkynes (Ag-AAC reaction) at room temperature or in the presence of heat (Scheme 8).[78]

In 2013, Guolin Cheng and co-workers reported the synthesis of 1,5-disubstituted triazoles *via* the three-component reaction of aliphatic amines, propynones, and tosyl azides (TsN_3) by a Michael addition/deacylative diazo transfer/cyclization sequence. The enamine intermediate formed in this method may exist in three tautomers, *i.e.*, iminoenol, iminoketone, and ketoenamine. The intermediate formed undergoes Regitz diazo transfer rearrangement, followed by 1,3-dipolar cycloaddition to yield 1,2,3-triazole derivatives (Scheme 9).[79]

A green synthetic route was reported for the preparation of 1,4-disubstituted 1,2,3-triazoles using a specific ionic liquid, 1-methyl-3-butylimidazolium hydroxide [Bmim]OH, *via* copper-catalysed azide alkyne cycloaddition reaction (CuAAC). This



Scheme 9 Synthesis of 1,2,3-triazoles *via* Michael addition/deacylative diazo transfer/cyclization sequence.

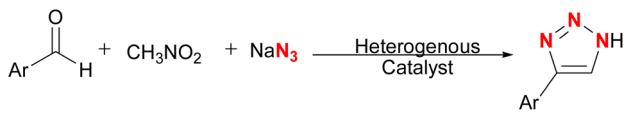


Scheme 10 Synthesis of 1,2,3-triazoles *via* copper-catalyzed azide alkyne cycloaddition (CuAAC).

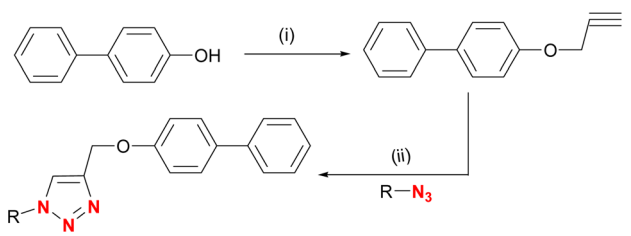
method for the synthesis of substituted 1,2,3-triazoles is highly regioselective and economical, as it gives excellent yields without using any bases, reducing agents, ligands or inert atmosphere. In addition to this, the one-pot, three-component copper-catalyzed azide alkyne cycloaddition (CuAAC) for the synthesis of 1,2,3-triazoles has been developed using alkyl bromide, terminal alkyne and sodium azide as starting materials in excellent yields (Scheme 10).[80]

The synthesis of 4-aryl–NH–1,2,3-triazoles *via* a multicomponent reaction involving various benzaldehydes, sodium azide, and nitromethane was developed. The acid properties of Al-MCM-41 and sulphated zirconia were used to develop this strategy. Between the catalyst and acids, acids decide the efficiency of the formed 4-aryl–NH–1,2,3-triazoles in the reaction. The reaction proceeds smoothly under mild conditions, affording excellent yields with high regioselectivity. The strong Brønsted and Lewis acidic sites of these solid catalysts play a crucial role in activating the carbonyl group and facilitating azide addition. Moreover, the heterogeneous nature of these materials allows the easy recovery and reuse of the catalyst, making the process economically and environmentally favourable. This methodology represents a green and efficient alternative to conventional metal-catalyzed systems for the preparation of substituted NH-triazoles (Scheme 11).[81]

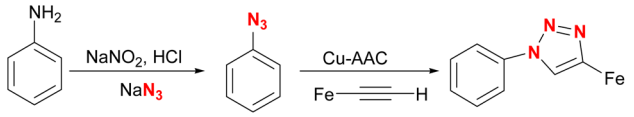
A novel synthetic method for the synthesis of 1,2,3-triazole derivatives in excellent yields by reacting *p*-hydroxy diphenyl



Scheme 11 Synthesis of 1,2,3-triazoles using a heterogenous catalyst.



Scheme 12 Synthesis of 1,2,3-triazoles from p-hydroxy diphenyl and propargyl bromide. (i) Propargyl bromide, K_2CO_3, DMF, 90%; (ii) CuI (1 mol%), $DHQD_2$(PHAL) (1 mol%), H_2O/DCM (1 : 1), RT, 0.5–2 h, 80–96%.



Scheme 13 Synthesis of 1,2,3-triazoles from sodium nitrate and azides.

with propargyl bromide and potassium carbonate, followed by copper-catalysed azide alkyne cycloaddition (CuAAC) was reported. A library of seventeen new 1,2,3-triazole derivatives was synthesised by this method in 2017 by Abdul Aziz Ali and co-workers. All seventeen compounds are popular owing to their anti-tubercular activity against *Mycobacterium tuberculosis* H37Ra (ATCC 25177 strain). Additionally, a few of them exhibited significant activity with a low minimum inhibitory concentration (MIC) (Scheme 12).[82]

A novel series of ferrocene-1*H*-1,2,3-triazole hybrid compounds was synthesised using the following method described by Ashanul Haque and co-workers in 2017. The reaction proceeds *via* the reaction between primary amines with sodium azides and sodium nitrate, followed by copper-catalysed azide alkyne cycloaddition (CuAAC) in the presence of iron acetylenes, forming ferrocene derivatives of 1,2,3-triazoles (Scheme 13).[83]

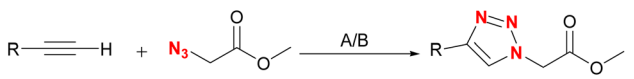
A very simple and efficient method for the synthesis of 1,4-disubstituted 1,2,3-triazoles was developed *via* Huisgen 1,3-dipolar cycloaddition between terminal alkynes and methyl 2-azidoacetate with Cu sources (CuI and $CuSO_4 \cdot 5H_2O$) as a catalyst in excellent yields at room temperature. The prepared 1,4-disubstituted 1,2,3-triazole derivatives act as excellent inhibitors for Src kinase (Scheme 14).[84]

A highly regioselective procedure for the synthesis of 1,5-disubstituted 1,2,3-triazole using the Er $(OTf)_3$/[mpy]OTf/H_2O catalytic system and a recyclable Lewis acid–ionic liquid–water medium was explained by Loredana Maiuolo in 2019. $Er(OTf)_3$ (erbium(III) trifluoromethanesulfonate), acted as a Lewis acid metal catalyst and [mpy]OTf (1-methylpyridinium trifluoromethanesulfonate), which is an ionic liquid, served as a solvent or co-catalyst medium. Water acts as a green solvent and sometimes assists in the catalytic cycle. The reaction proceeds through an eliminative azide-olefin cycloaddition (EAOC), offering a good yield ranging from 80–90%. The main advantages of this reported method are the usage of the catalyst for 5 consecutive times without changes in the yield of the 1,2,3-triazoles formed in all the procedures (Scheme 15).[85]

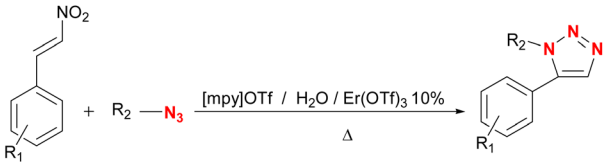
A silver metal-mediated one-pot three-component cycloaddition reaction for the synthesis of 1-*N*-vinyl-substituted 1,2,3-triazoles was reported in 2019 by Jinpeng Chen and co-workers. This reaction proceeds *via* the cycloaddition of phenylacetylenes, trimethylsilylazide, and 1,3-dicarbonyl compounds in the presence of silver salts such as silver(II) sulfate ($AgSO_4$) and sodium bicarbonate ($NaHCO_3$) to yield two different types of 1,2,3-triazoles derivatives in a 52 : 48 ratio. This method does not need any preinstallation of vinyl azide precursors, which make this scheme simple and practical (Scheme 16).[86]

An interesting method was reported for the synthesis of triazoles using polymer support copper azide nanoparticles (CANP), which act as both the catalyst and reagent, using substituted benzyl bromides and terminal alkynes as starting materials. Two different substituted triazoles are formed based on the starting material used. 5-Alkynyl 1,4-disubstituted triazoles are formed by the terminal alkyne containing an electron-donating group (EDG) and 1,4-disubstituted triazoles are formed by the alkyne molecule containing a terminal electron-withdrawing group (EWG) (Scheme 17).[87]

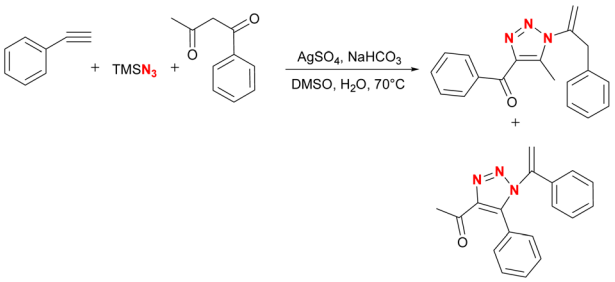
In 2021, Mohammad Sadegh Asgari and co-workers developed a novel route for the synthesis of 1,2,3-triazole derivatives containing amide and aryloxy groups *via* copper-catalysed azide alkyne cycloaddition and one-pot sequential hydroxylation *O*-



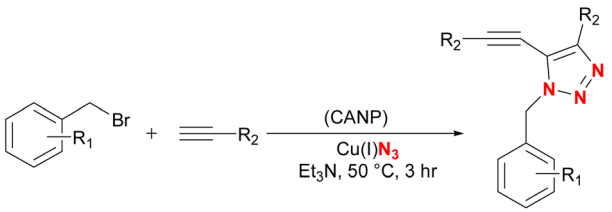
Scheme 14 Synthesis of 1,2,3-triazoles *via* cycloaddition between terminal alkynes and methyl 2-azidoacetate with Cu sources. (A) CuI (5 mol%) Na ascorbate, tBuOH/H_2O (1/1, v/v), RT 12–72 h; (B) $CuSO_4 \cdot 5H_2O$ (5 mol%) Na ascorbate (10 mol%), aq. PEG400-H_2O (1/1, v/v), RT 1–8 h.



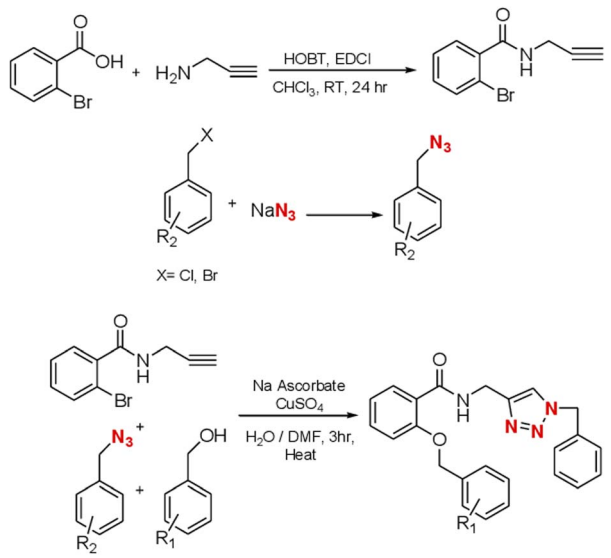
Scheme 15 Synthesis of 1,2,3-triazoles using the $Er(OTf)_3$/[mpy]OTf/H_2O catalytic system.



Scheme 16 Synthesis of 1,2,3-triazoles *via* the cycloaddition of phenylacetylenes, trimethylsilylazide, and 1,3-dicarbonyl compounds.



Scheme 17 Synthesis of 1,2,3-triazoles using polymer support copper azide nanoparticles (CANPs).

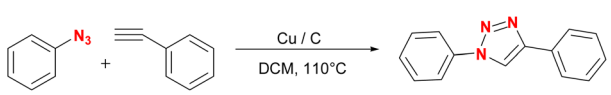


Scheme 18 Synthesis of 1,2,3-triazoles containing amide and aryloxy groups.

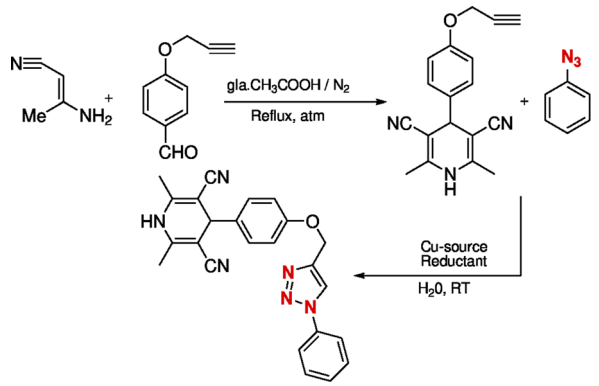
alkylation and click reaction of 2-bromo-*N*-prop-2-ynyl-benzamides. The in situ-prepared phenol moiety in H_2O/DMF as the solvent/co-solvent system prompted them to perform the reaction between benzyl halide and phenols. The synthetic method involves the use of 2-bromo-*N*-prop-2-ynyl-benzamide and various benzyl halides *via* a one-pot copper-catalyzed hydroxylation-*O*-alkylation/click reaction. The yield of triazoles formed using this method was excellent, making the procedure economically important (Scheme 18).[88]

A very simple and easy method for the synthesis of 1-monosubstituted and 1,4-disubstituted 1*H*-1,2,3-triazoles was established under continuous flow conditions using copper-on-charcoal as a heterogeneous catalyst. 2-Ynoic acids were also used in this reaction as small-chain alkyne donors in a decarboxylation/cycloaddition cascade, which allow the use of gaseous reagents to be bypassed, delivering the desired triazoles in excellent yields. This novel methodology found its importance in the synthesis of rufinamide, an antiepileptic agent, in 96% isolated yield (Scheme 19).[89]

In 2022, Sabera Bijani and co-workers synthesised biologically active compounds containing a triazole moiety to fight cancer. The synthesis of the biologically active anticancer, antiproliferative compound (6-dimethyl-substituted-(((1*H*-1,2,3-triazole-4-yl)methoxy)phenyl)-1,4-dihydropyridine-3,5-dicarbonitrile involves the reaction between 3-aminobut-2-enenitrile and 4-(prop-2-ynyloxy)benzaldehyde, which forms an intermediate, followed by reaction with azido benzene in the presence of a copper catalyst at room temperature. The formed



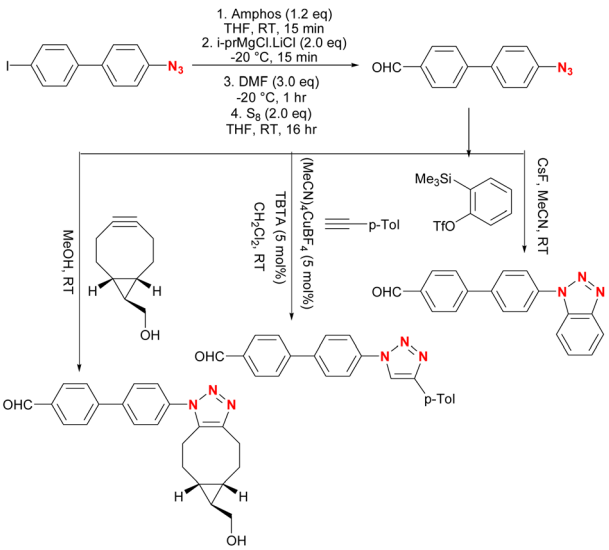
Scheme 19 Synthesis of 1,2,3-triazoles using copper-on-charcoal as a heterogeneous catalyst.



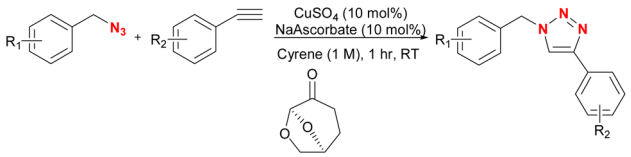
Scheme 20 Synthesis of 1,2,3-triazoles from 3-aminobut-2-enenitrile, 4-(prop-2-ynyloxy)benzaldehyde and azide.

substituted 1,2,3-triazole derivates were found to have excellent anticancer activities and cytotoxic potential on colorectal adenocarcinoma (Caco-2) cell lines (Scheme 20).[90]

An efficient method was reported by Rina Namioka and co-authors in 2023 for the synthesis of triazoles *via* organo-magnesium intermediates having a protected azido group. This method proceeds *via* protection of azido groups with di-(*tert*-butyl)(4-(dimethylamino)phenylphosphine) (amphos), and subsequently iodine–magnesium exchange for the preparation of organo-magnesium intermediates, which further react with alkynes to form 1,2,3-triazoles. Various azides were successfully synthesized by the Grignard reaction of carbanions having phosphazide moieties with various electrophiles, followed by deprotection with elemental sulfur. They are currently engaged in further studies, including the preparation and transformation of carbanions with phosphazide moieties (Scheme 21).[91]



Scheme 21 Synthesis of triazoles *via* organo-magnesium intermediates.

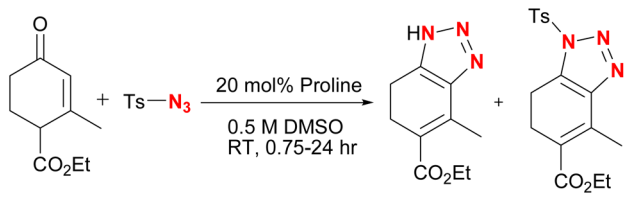


Scheme 22 Synthesis of 1,2,3-triazoles from copper-catalyzed azide alkyne cycloaddition (CuAAC) using Cyrene™.

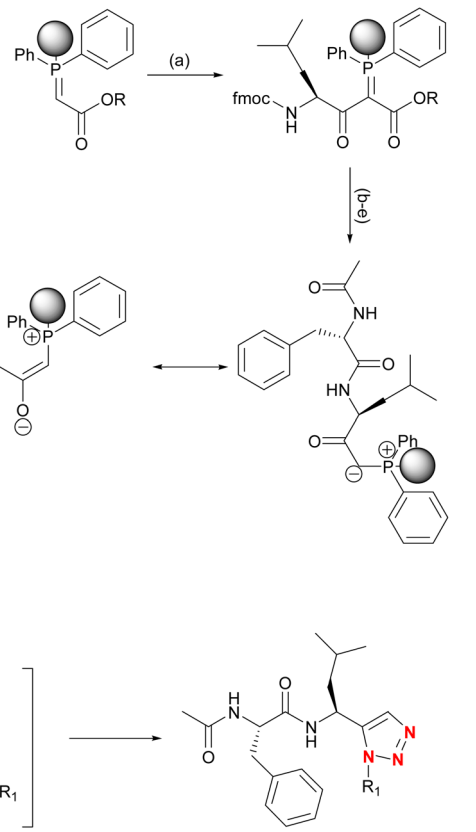
A green method for the synthesis of 1,2,3-triazoles *via* copper-catalyzed azide alkyne cycloaddition (CuAAC) using Cyrene™ as a biodegradable and non-toxic solvent was developed by Andrea Citarella and co-authors in 2025. This method allows product isolation by simple precipitation in water, eliminating the need for organic solvent extractions and column chromatography purification, thus minimizing waste consumption. Also, this protocol is amenable to a three-component reaction involving organic halides, terminal acetylenes and sodium azide, thus improving the safety of the process and expanding its potential for eco-friendly synthetic applications (Scheme 22).[92]

3.1.2 Using non-metal sources as catalysts. The unexpected discovery of NH-1,2,3-triazoles was detected by Dhevalapally B. Ramachary and his co-workers in 2008. Their main focus was on the amine-mediated *in situ* generation and application of novel push–pull dienamines/push–pull dienols. In this process, they expected to generate protected 1,2,3-triazoles from various organic halides in an amino/amine acid-catalyzed coupling reaction. They expected that organic azide couples with the in situ-generated push–pull dienamines to produce protected 1,2,3-triazoles. However, instead of protected 1,2,3-triazoles, they produced NH-1,2,3-triazoles, making this reaction a novel approach for the synthesis of NH-1,2,3-triazoles from organic azides in the presence of organo-catalysts (Scheme 23).[93]

A new synthetic technique for the synthesis of peptide derivatives of triazoles was designed by Ahsanullah and co-workers in 2009. This method involves the solid-phase synthesis of 5-peptidyl-(1*H*-1,2,3-triazol-1-yl) peptides from polymer-supported phosphoranylidene acetate as the starting material. Fmoc-protected amino acids have been shown to yield Fmoc-amino acyl phosphoranylidene acetates *via* racemization-free *C*-alkylation of polymer-bound phosphoranylidene acetates, which on further deprotection by Fmoc cleavage, the peptides are elongated *via* the free amino group by standard peptide chemistry. This is followed by the deprotection of the TMSE (trimethyl silyl ether) or *t*-butyl ester group, forming



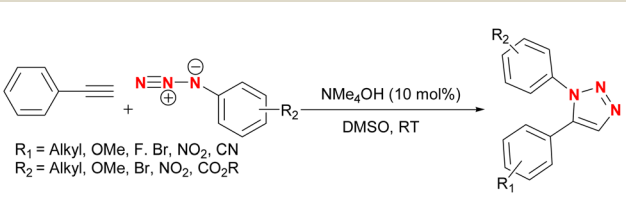
Scheme 23 Synthesis of 1,2,3-triazoles *via* a push–pull dienol reaction.



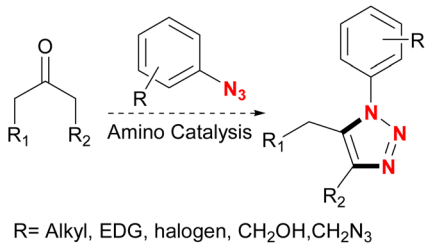
Scheme 24 Synthesis of peptide derivatives of 1,2,3-triazoles. (a) Fmoc-Leu-OH and MSNT, lutidine in CH_2Cl_2 or BTFFH, DIPEA, DMF (R = TMSE or tertbutyl), 14 h; (b) 20% piperidine/DMF; (c) Fmoc-Phe-OH, DIC, HOBT, DMF, 2 h; (d) 20% Ac_2O/DMF or (e) TAS-F/DMF or TFA/CH_2Cl_2 (R = TMSE or tertbutyl); and (f) 4–14, CH_2Cl_2, or THF.

decarboxylated peptidyl phosphorane. The formed decarboxylated peptidyl phosphorane was reacted with 4-toluenesulfonyl azide at room temperature to form 5-peptidyl-(1*H*-1,2,3-triazol-1-yl) tosylate in high yield. The reaction proceeds under metal-free conditions with high regioselectivity (Scheme 24).[94]

A very simple and easy method for the synthesis of substituted 1,2,3-triazoles was reported in 2010 by Sen W. Kwok and co-workers. Triazoles are formed in excellent yields using this method. The synthesis of 1,5-diarylsubstituted 1,2,3-triazoles was done by reacting terminal and azides in DMSO solvent in the presence of catalytic tetraalkylammonium hydroxide. This reaction requires mild conditions, and therefore it is easy to synthesise triazoles *via* this method (Scheme 25).[95]



Scheme 25 Synthesis of 1,2,3-triazoles *via* azide–alkyne cycloaddition.

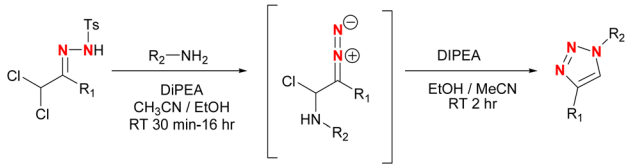


Scheme 26 Synthesis of 1,2,3-triazoles from unactivated ketones.

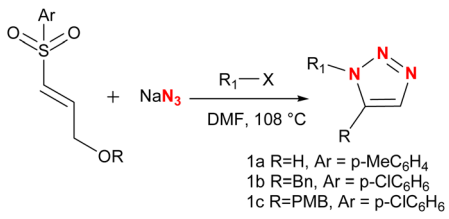
A very interesting approach for the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles with enamides formed *in situ* from unactivated ketones (β-ketoesters, β-ketonitriles or β-diketones) and a secondary amine in catalytic quantity was proposed by Mokhtaria Belkheira and co-workers in 2011. The reaction proceeds *via* the cycloaddition of enamides formed *in situ* and arylazides. The reaction possesses high regioselectivity and chemo-selectivity (Scheme 26).[96]

A novel method for the synthesis of 1,2,3-triazoles was developed *via* the Sakai triazole formation reaction. It involves the condensation of a primary amine and an α,α-dichloro tosylhydrazone to form 1,4-substituted 1,2,3-triazole regioselectively under ambient reaction conditions. Given that this reaction proceeds in a highly chemoselective manner, the use of a protecting group seems to be unnecessary. The reactions were performed either in a solvent mixture of acetonitrile and ethanol (1 : 1 v/v%) or in methanol, in the presence of six equivalents of *N*,*N*-diisopropylethylamine (DIPEA) (Scheme 27).[97]

A metal-free, regioselective, one-pot, three-component approach for the synthesis of substituted 1,2,3-triazoles was developed by Santu Dey and Tanmaya Pathak in 2014. By combining vinyl sulfones, sodium azide and alkyl bromides, tosylates, mesylates or aryl amines, and iodides under metal-free conditions produce 1,5-disubstituted 1,2,3-triazoles in good to excellent yields. The organic azides generated *in situ* react with vinyl sulfones in a regioselective fashion in the absence of metal ions. This method is capable of generating alkyl/alkyl-, alkyl/aryl- and aryl/aryl-containing 1,5-disubstituted 1,2,3-triazoles under simple reaction conditions (Scheme 28).[98]

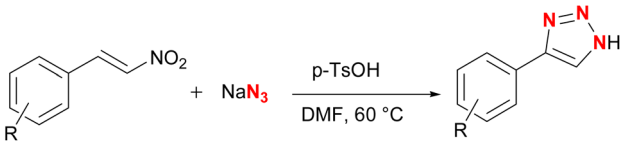


Scheme 27 Synthesis of 1,2,3-triazoles from the Sakai triazole formation.



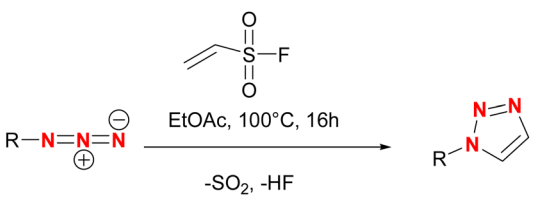
Scheme 28 Synthesis of 1,2,3-traizoles from vinyl sulfones and sodium azide.

A novel method for the synthesis of 4-aryl–NH–1,2,3-triazoles was developed by Xue-JingQuan and co-workers in 2014 using *p*-toluenesulfonic acid. The reaction proceeds through the 1,3-dipolar cycloaddition between nitro olefins and sodium azides for the synthesis of 4-aryl–NH–1,2,3-triazoles in good to high yields. The use of *p*-TsOH as a catalyst made this method a new and novel technique for the synthesis of substituted 1,2,3-triazoles. This process avoids the use of any metal catalyst, offering a cleaner and more environmentally benign route. Moreover, its operational simplicity and wide substrate compatibility make it an efficient alternative to conventional metal-catalyzed approaches (Scheme 29).[99]

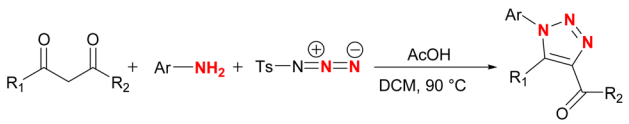


Scheme 29 Synthesis of 1,2,3-triazoles from nitro olefins and azides.

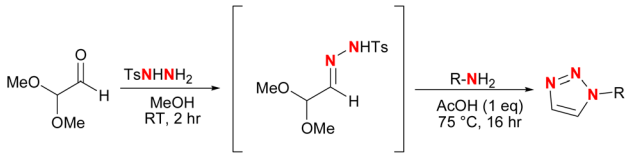
It was surprisingly challenging for chemists to synthesise 1-substituted triazoles. This method reports a simple and straightforward click-inspired protocol for the synthesis of 1-substituted-1,2,3-triazoles from organic azides and a stable acetylene-surrogate, ethenesulfonyl fluoride (ESF) in the presence of ethyl acetate at 100 °C. This reaction proceeds efficiently under mild and metal-free conditions, affording excellent yields with broad substrate compatibility. The operational simplicity and avoidance of gaseous alkynes make this approach a practical alternative to traditional CuAAC-based strategies (Scheme 30).[100]



Scheme 30 Synthesis of 1,2,3-triazoles from organic azides and stable acetylene-surrogate.



Scheme 31 Synthesis of 1,2,3-triazoles from primary amines, tosyl azides and 1,3-dicarbonyls.

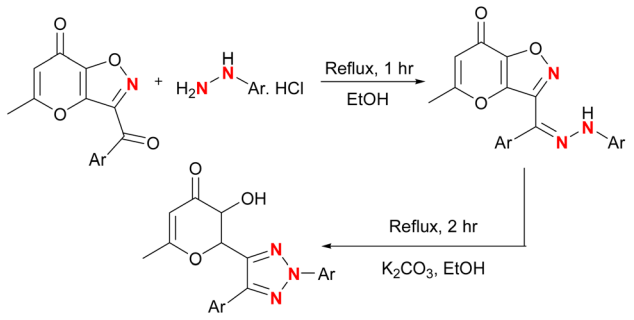


Scheme 32 Synthesis of 1,2,3-triazoles from tosyl hydrazide, primary amine and 2,2-dimethoxyacetaldehyde.

A simple and easy method for the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles was developed *via* the reaction among readily available primary amines, tosyl azides and 1,3-dicarbonyls as starting materials. This reaction proceeds *via* cycloaddition reaction under metal-free conditions in the presence of a simple organic acid (acetic acid) and dichloromethane solvent in moderate to excellent yields. This protocol offers high regioselectivity and functional group tolerance, making it suitable for diverse substrate scopes. The mild reaction conditions and absence of metal catalysts further enhance its green and sustainable synthetic applicability (Scheme 31).[101]

A simple and efficient route was developed for the three-component synthesis of 1-substituted 1,2,3-triazoles using a primary amine and tosyl hydrazide as nitrogen sources and 2,2-dimethoxyacetaldehyde as a carbon source. This proceeds smoothly with various primary amines including both aliphatic and aniline and is tolerant to a wide range of functional groups such as electron-rich and electron-deficient aryl groups, terminal alkynes, carbonyls and sterically crowded primary amines. This reaction proceeds with a yield ranging from good to excellent (Scheme 32).[102]

A general method for the synthesis of substituted 1,2,3-triazoles bearing an allomaltol fragment was elaborated by Constantine V. Milyutin and co-authors in 2024. This method proceeds *via* the interaction of aroyl-containing pyrano[2,3-*d*] isoxazolone derivatives with various hydrazines to form appropriate hydrazones followed by Boulton–Katritzky rearrangement. This method was unsuccessful for the synthesis of 1,2,3-triazoles with aliphatic hydrazines and unsubstituted hydrazine, as they lead to the opening of the pyranone ring and pyrazolylisoxazoles were produced as a result of recyclization (Scheme 33).[103]



Scheme 33 Synthesis of substituted 1,2,3-triazoles bearing an allomaltol fragment.

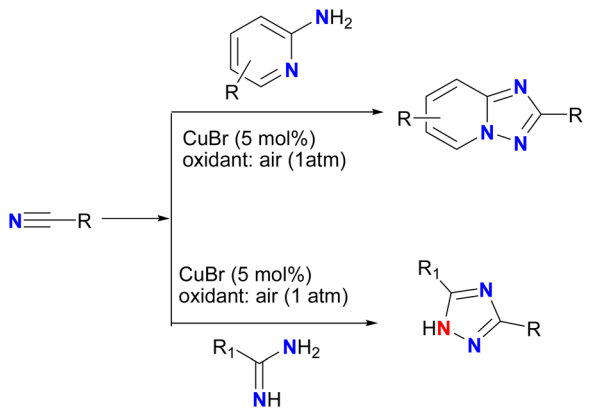
3.2 Synthesis of 1,2,4-triazole analogues

The 1,2,4-triazole ring is a vital and versatile heterocyclic moiety, serving as a key functional group in aromatic compounds. Its exceptional stability and diverse reactivity make it an important scaffold in drug discovery and materials science. 1,2,4-Triazole-based molecules have attracted significant attention in organic chemistry due to their diverse and versatile nature.

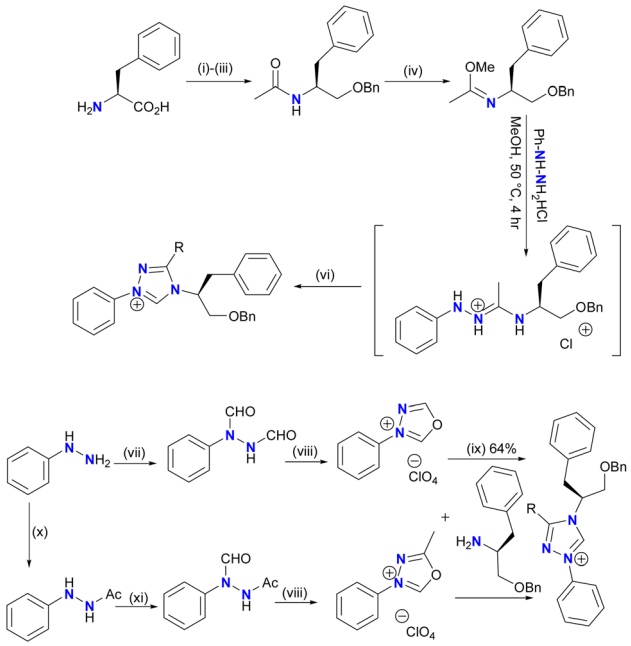
3.2.1 Using metal source as catalyst. Satoshi Ueda and Hideko Nagasawa reported the single-step elaboration of 1,2,4-triazole structures using a conceptually distinct copper-catalysed oxidative coupling approach. This method proceeds *via* the direct synthesis of the 1,2,4-triazole nucleus by reacting 2-aminopyridines and nitriles involving transition metal-catalysed N–C bond formation and oxidative N–N coupling. By the addition of 10 mol% zinc iodide to the above-mentioned reaction, it greatly improved the reaction efficacy and yield percentage (Scheme 34).[104]

The following reported method describes the preparation of new chiral *N*,*N*-disubstituted 1,2,4-triazolium-based *N*-heterocyclic carbene (NHC) salt precursors. The reaction of L-phenylalanine *via* the corresponding imino ether and acetohydrazonamide gives 1,3,4-trisubstituted triazolium salt by stepwise ring construction. Alternatively, the heterocyclic *O*-/*N*-heteroatom exchange strategy based on ring-opening/ring-closure of the oxadiazolium precursor produces the 1,4-disubstituted 1,2,4-triazolium salt. This work describes the conditions and strategies for two different methods (Scheme 35).[105]

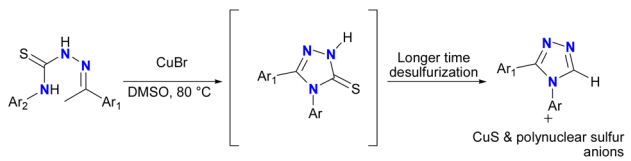
Selective C–N bond formation *via* C–S bond for the construction of 4,5-disubstituted 1,2,4-triazole-3-thiones from various arylidene-aryl thiosemicarbazides catalyzed by Cu(II) was reported in the following method. Desulfurization of 1,2,4-triazole-3-thiones is assisted by thiophilic copper (Cu) to provide 1,2,4-triazoles with concomitant formation of copper(II) sulfide (CuS) and polynuclear sulphur anions. Two classes of heterocyclic compounds, 4,5-disubstituted 1,2,4-triazole-3-thiones and 4,5-disubstituted 1,2,4-triazoles, can be synthesized using the above-mentioned process by simply adjusting the reaction time (Scheme 36).[106]



Scheme 34 Synthesis of 1,2,4-triazoles from 2-aminopyridines and nitriles.

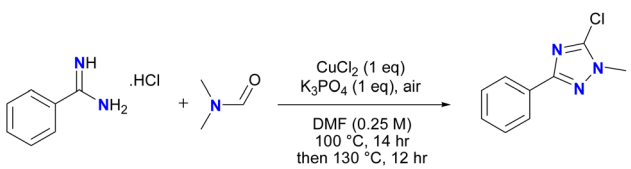


Scheme 35 Synthesis of 1,2,4-triazoles from L-phenylalanine and acetohydrazonamide. (i) $LiAlH_4$, THF, 95%; (ii) NaH, BnBr, THF, reflux, 16 h, 60%; (iii) Ac_2O, EtOAc, RT, 2.5 h, 100%; (iv) Me_3OBF_4, DCM, RT, 49%; (v) Ph–NH–NH_2HCl, MeOH, 50 °C, 4 h; (vi) $HC(OMe)_3$, MeOH, 80 °C, overnight; (vii) HCO_2H, 18 h, 80 °C, 73%; (viii) Ac_2O, $HClO_4$, 80–84%; (ix) AcOH, 1.5 h, 110 °C, 64%; (x) AcOH, 3.5 h, 80 °C, 96%; and (xi) HCO_2H, 15 h, 50 °C, 79%.

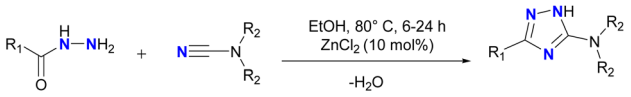


Scheme 36 Synthesis of 1,2,4-triazoles *via* C–N bond formation.

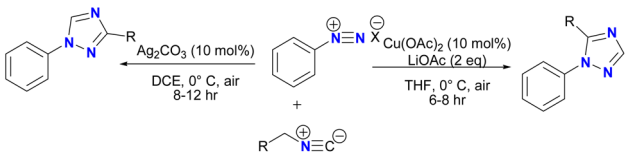
A simple one-pot synthesis for the construction of 1,3-disubstituted 1,2,4-triazoles from amidines with trialkylamines and DMF involving a copper catalyst, tripotassium phosphate (K_3PO_4) as the base, and oxygen (O_2) as the oxidant, was developed by Huawen Huang and co-workers in 2015. This method is versatile in nature as it can synthesise derivatives of both 1,2,4-triazoles and 1,3,5-triazines with the same starting materials but different reaction conditions. In the presence of DMF, 1,3-disubstituted 1,2,4-triazoles are formed, whereas in the presence of dimethyl sulfoxide (DMSO), 2,4,6-trisubstituted and 2,6-disubstituted 1,3,5-triazines are formed (Scheme 37).[107]



Scheme 37 Synthesis of 1,2,4-triazoles from amidines and trialkylamines.



Scheme 38 Synthesis of 1,2,4-triazoles *via* the coupling of acyl hydrazides and dialkylcyanamides.

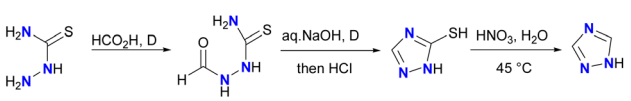


Scheme 39 Synthesis of 1,2,4-triazoles from isocyanides and diazonium salts.

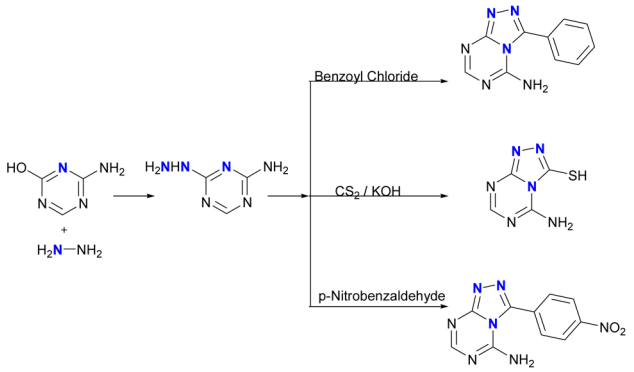
A straightforward and high yielding approach for the synthesis of 3 dialkylamino-1,2,4-triazoles was developed by coupling acyl hydrazides and dialkylcyanamides in ethanol *via* zinc(II)-catalyzed (10 mol% $ZnCl_2$). This study explains the effects of substituents on the rate of the reaction. Steric hindrance on acyl hydrazide reduces the reaction rate without affecting the yield of the heterocycles, whereas electronic effects of substituents at the acyl hydrazide moiety do not significantly affect the reaction rate and the yield of the target triazoles (Scheme 38).[108]

A very interesting and simple method for the synthesis of 1,3-disubstituted and 1,5-disubstituted triazoles from isocyanides and diazonium salts was reported in 2018 by Jian-Quan Liu and co-workers. This method allows the construction of 1,3-disubstituted and 1,5-disubstituted triazoles, proceeding *via* the catalyst-dependent regioselective [3 + 2] cycloaddition of diazonium salts and isocyanides in the presence of Cu(II) and Ag(I) catalyst, respectively. This catalytic methodology enables the modular, controlled and facile synthesis of 1,2,4-triazoles with high efficiency and excellent group compatibility (Scheme 39).[109]

3.2.2 Using non-metal sources as catalyst. A method for the synthesis of 1,2,4-triazoles was developed by C. Ainsworth *via* the reaction of thiosemicarbazide and formic acid, followed by oxidation. This procedure is no longer regarded as the best method available for the preparation of 1,2,4-triazoles. However, it represents one of the earliest and most fundamental approaches that established the core reactivity pattern of thiosemicarbazide toward ring closure and heterocycle formation. This reaction laid the groundwork for subsequent modifications, leading to more efficient, selective, and



Scheme 40 Synthesis of 1,2,4-triazoles *via* the oxidation of thiosemicarbazide and formic acid.



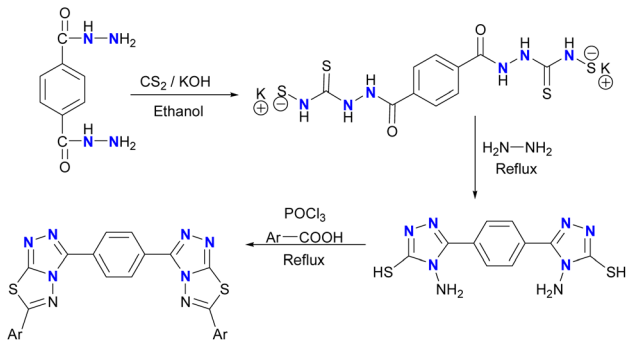
Scheme 41 Synthesis of 1,2,4-triazoles from 2-amino-4-hydroxy-1,3,5-triazine and hydrazine hydrate.

environmentally benign methodologies. Although replaced by advanced catalytic and solvent-assisted techniques, Ainsworth's method provides valuable mechanistic insight into the cyclization behaviour and structural evolution of 1,2,4-triazole frameworks, thus contributing significantly to the historical development and understanding of triazole chemistry (Scheme 40).[110]

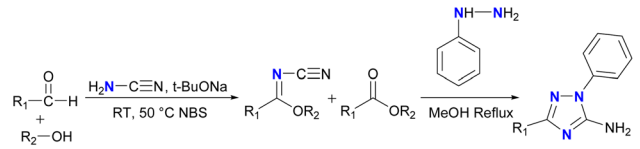
A library of compounds was synthesised by heating 2-amino-4-hydroxy-1,3,5-triazine with hydrazine hydrate, which forms the intermediate 2-amino-4-hydrazino 1,3,5-triazine, followed by cyclo-condensation with carbon disulphide (CS_2), 4-nitrobenzaldehyde (4-(NO_2)–C_6H_4CHO) and benzoyl chloride (C_6H_5COCl), giving the respective 1,2,4-triazole derivatives. This method is very efficient for the synthesis of various 1,2,4-triazole derivatives in good yield (Scheme 41).[111]

A multistep reaction sequence for the synthesis of 1,4-bis (6-(substituted phenyl)-[1,2,4]-triazolo[3,4-*b*]-1,3,4-thiadiazole) derivatives from terephthalic dihydrazide was developed by Vikrant S. Palekar and co-workers in 2009. The starting material of the reaction terephthalic dihydrazide was prepared from poly(ethylene terephthalate) waste *via* reaction with hydrazine hydrate in good yield (86%). The triazole derivatives obtained in this method showed potential antibacterial activity against various bacteria and fungi (Scheme 42).[112]

The development of an efficient and convenient procedure for the synthesis of 1,2,4-triazole derivatives *via* the



Scheme 42 Synthesis of 1,2,4-triazoles from terephthalic dihydrazide.

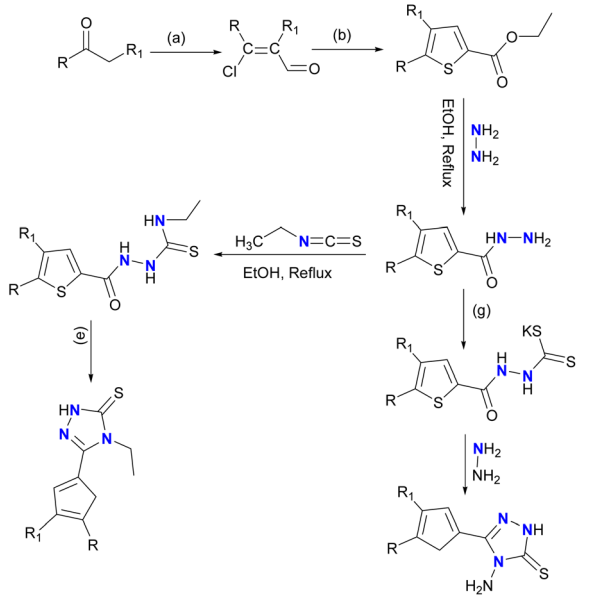


Scheme 43 Synthesis of 1,2,4-triazoles *via* the cyanoimidation of aldehydes.

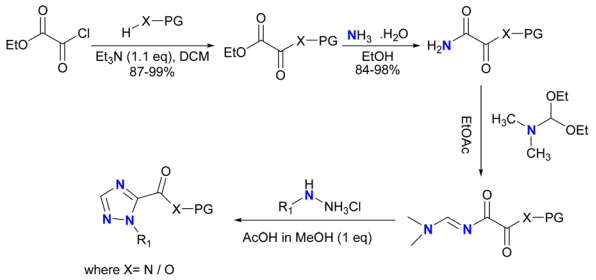
cyanoimidation of aldehydes using cyanamide as a nitrogen source and *N*-bromo succinimide (NBS) as an oxidizing agent was achieved in the absence of a catalyst. This technique was proposed by Ping Yin and co-workers in 2009. The reaction proceeds *via* one-pot synthesis under mild reactions conditions and using inexpensive reagents. The formation of intermolecular C–N and C–O bonds is the key step, which subsequently undergo cyclization reaction to give 1,2,4-triazole derivatives in high yields (Scheme 43).[113]

An efficient and versatile method for the synthesis of 1,2,4-triazole derivatives with the same starting materials and different reaction conditions was described by Anelia Ts. Mavrova and co-workers in 2009. This method allows the synthesis of derivatives of 4,5-substituted-1,2,4-triazole-thiones and 2,5-substituted-1,3,4-thiadiazoles using a simple carbonyl as the starting material. Hydrazine hydrate and ethyl isothiocyanate are used as a nitrogen source. The formed derivatives exhibited excellent cytotoxicity *in vitro* against thymocytes (Scheme 44).[114]

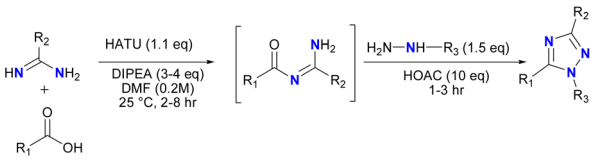
Another simple and general method for the synthesis of 1,5-disubstituted-1,2,4-triazoles was developed by Yingju Xu and co-workers in 2010. A series of oxamide-derived amidine reagents were accessed in excellent yields. Typically, these amidine reagents are stable crystalline solids, which are reacted with



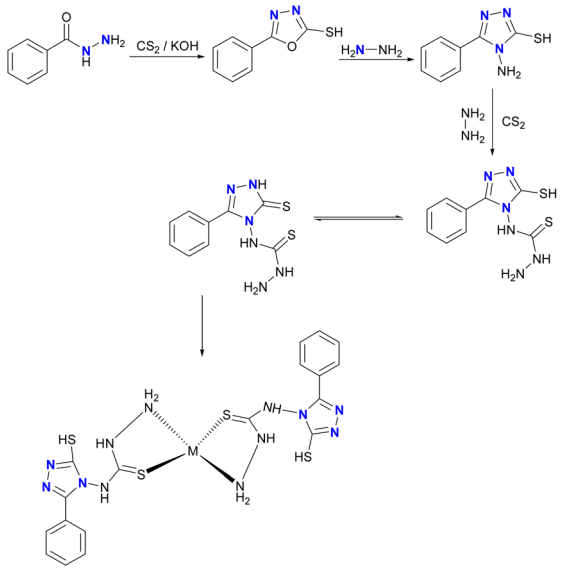
Scheme 44 Synthesis of 1,2,4-triazoles from simple carbonyls. (a) DMF, $POCl_3$, trichloroethylene; (b) thioglycolate, triethylamine, pyridine, 15 °C; (e) 10% NaOH, reflux; (f) conc. H_2SO_4, 0 °C; and (g) NaOH, CS_2, absolute EtOH.



Scheme 45 Synthesis of 1,2,4-triazoles from oxamide-derived amidine reagents.



Scheme 46 Synthesis of 1,2,4-triazoles from carboxylic acids and primary amidines.

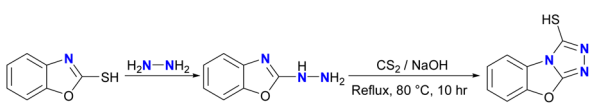


Scheme 48 Synthesis of 1,2,4-triazoles *via* the condensation of 4-amino-5-phenyl-4*H*-1,2,4-triazole-3 thiol and thiosemicarbazide.

various hydrazine hydrochloride salts to generate the targeted 1,2,4-triazole derivatives under very mild reaction conditions. This reaction is versatile in nature as both the aromatic and aliphatic hydrazines are readily reacted with amidine reagents, delivering the 1,5-disubstituted 1,2,4-triazoles derivatives in excellent yields (Scheme 45).[115]

A simple method was developed by Georgette M. Castanedo and co-workers in 2010 for the synthesis of 1,3,5-trisubstituted 1,2,4-triazoles from primary amidines, carboxylic acids and monosubstituted hydrazines using O-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) as an organic coupling reagent. This reaction is highly regioselective and proceeds *via* one-pot synthesis, with mild reaction conditions to provide various 1,2,4-triazole derivatives (Scheme 46).[116]

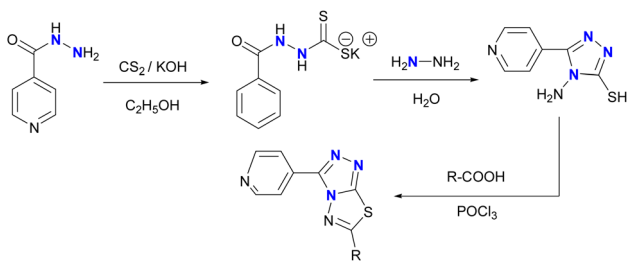
A rapid and operationally simple method for the synthesis of 1,2,4-triazole derivatives was developed by Huda A. Hassan and co-workers in 2012. This method involves the preparation of benzoxazole by reacting a 2-hydrazino mixture of 2-mercapto benzoxazole and hydrazine hydrate obtained from Fluka or BDH. It further undergoes condensation in the presence of carbon disulphide (CS_2) and sodium hydroxide (NaOH), giving 1,2,4-triazole [4,3-*b*] benzoxazole-1-(2*H*) thione. This reaction proceeds efficiently under mild basic conditions, promoting cyclization and thione formation in good yield. The resulting fused triazole–benzoxazole system exhibits potential biological relevance due to its conjugated heterocyclic framework (Scheme 47).[117]



Scheme 47 Synthesis of 1,2,4-triazoles *via* the condensation of benzoxazole, carbon disulphide and sodium hydroxide.

A convenient and easy method for the synthesis of triazole *N*-(3-mercapto-5-phenyl-4*H*-1,2,4-triazol-4-yl) hydrazinecarbothioamide was developed *via* the condensation of 4-amino-5-phenyl-4*H*-1,2,4-triazole-3 thiol and thiosemicarbazide. In this method, 5-phenyl-1,3,4-oxadiazol-2-ylamine was synthesised by the relaxation of benzoic hydrazide, carbon disulphide (CS_2) and potassium hydroxide (KOH), which on further treatment with hydrazine and absolute alcohol forms 4-amino-5-phenyl-4*H*-1,2,4-triazole-3-thiol. The so-formed 4-amino-5-phenyl-4*H*-1,2,4-triazole-3-thiol on reaction with excess hydrazine in the presence of carbon disulphide (CS_2) forms *N*-(3-mercapto-5-phenyl-4*H*-1,2,4-triazol-4-yl)hydrazinecarbothioamide ligand. This ligand can bind with transition metal atoms such as copper(II) and nickel(II) to form triazole ligand complex compounds (Scheme 48).[118]

In 2021, D. K. Ramesh and co-workers synthesised 1,2,4-triazoles *via* the treatment of potassium dithiocarbazinate of isonicotinic acid hydrazide with hydrazine hydrate. They were further treated with various carboxylic acids to get series of novel 6-(substituted)-3-(pyridin-4-yl)-[1,2,4]-triazolo[3,4-*b*]

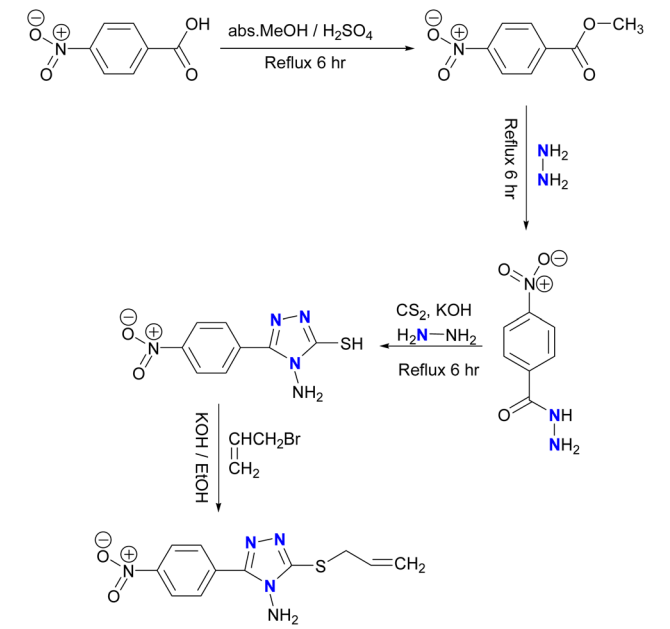


Scheme 49 Synthesis of 1,2,4-triazoles from isonicotinic acid hydrazide.

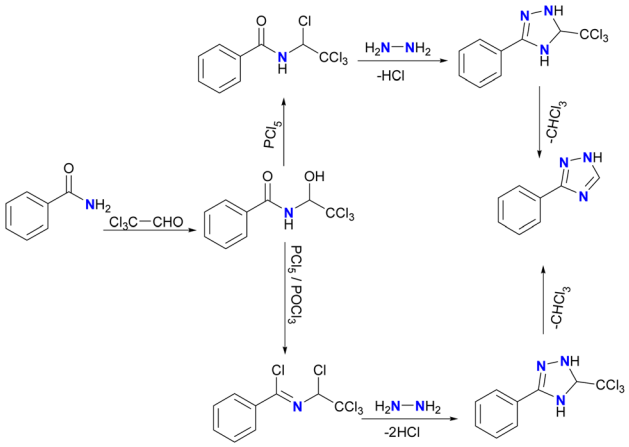
thiadiazole derivatives of 1,2,4-triazoles, which exhibited excellent antibacterial activity against *Staphylococcus aureus* and *Bacillus subtilis* (Scheme 49).[119]

A very easy and simple method for the synthesis of 5-(4-nitrophenyl)-4-amino-3-mercapto propenyl-1,2,4-triazole was reported in 2014 by Mahasin Alias and co-workers. In this method, 3-(4-nitrobenzoyl) dithiocarbazate was synthesised *via* the reaction of 4-nitrobenzoic acid with concentrated sulphuric acid, followed by reaction with hydrazine hydrate. On further reaction with carbon disulphide and a mixture of potassium hydroxide and absolute ethanol, it forms 3-(4-nitrobenzoyl)dithiocarbazate. The formed 3-(4-nitrobenzoyl)dithiocarbazate on treatment with excess hydrazine hydrate forms 5-(4-nitrophenyl)-4-amino-3 mercapto-1,2,4-triazole. Subsequent treatment with allyl bromide in the presence of a mixture of potassium hydroxide and absolute ethanol forms 5-(4-nitrophenyl)-4-amino-3-mercapto propenyl-1,2,4-triazole. The so-formed 5-(4-nitrophenyl)-4-amino-3-mercapto propenyl-1,2,4-triazole is used for the synthesis of metal complexes of Co(II), Ni(II), Cu(II), Zn(II), Au(III) and more (Scheme 50).[120]

A simple and convenient method for the synthesis of 3-aryl-1,2,4-triazoles was described by Antonio Guirado and co-workers in 2016. In this approach, chloralamides were prepared *via* the reaction between benzamides and chloral hydrate in high yields. On further treatment with a mixture of phosphorus pentachloride (PCl_5)/phosphorous oxychloride ($POCl_3$), they undergo conversion to (1,2,2,2-tetrachloroethyl) benzimidoyl chlorides, followed by reaction with hydrazine hydrate to give 3-aryl-1,2,4-triazoles in high to quantitative yields. The reaction proceeds *via* a double condensation reaction, followed by the spontaneous β-elimination of chloroform (Scheme 51).[121]

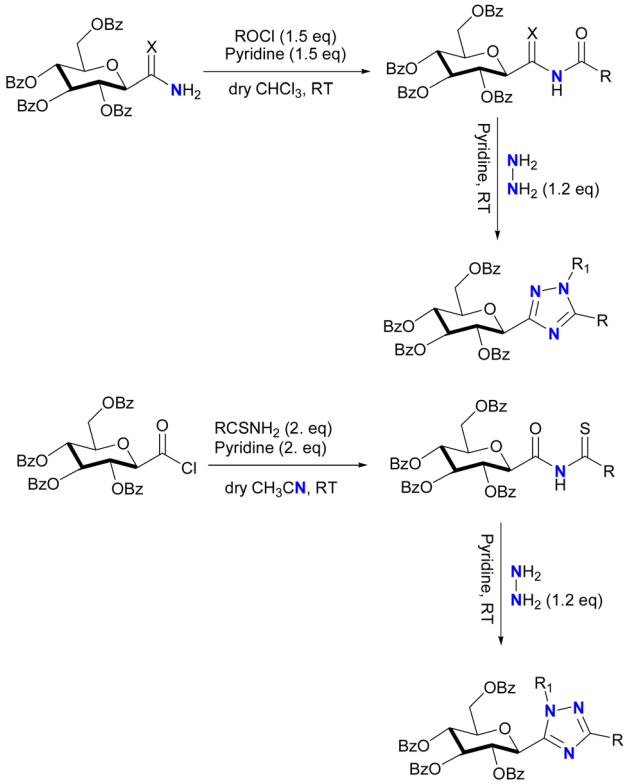


Scheme 50 Synthesis of 1,2,4-triazoles from 3-(4-nitrobenzoyl) dithiocarbazate.

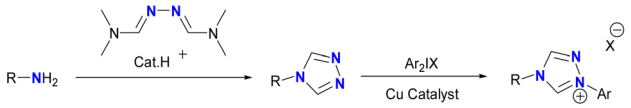


Scheme 51 Synthesis of 1,2,4-triazoles from chloralamides.

A typical route for the synthesis of 1,2,4-triazole derivatives containing *C*-glycopyranosyl was described by Katalin E. Szabó and co-workers in 2017. *O*-Perbenzoylated 2,6-anhydro-D-*glycero*-D-gulo-heptonothioamide on acylation with acid chlorides of thioamides by *O*-perbenzoylated 2,6-anhydro-D-*glycero*-D-gulo-heptonoyl chloride gives *N*-acyl-thioamide derivatives. These precursors further undergo regioselective reaction with substituted hydrazines to give 3-β-D-glucopyranosyl-1,5-disubstituted- and 5-β-D-glucopyranosyl-1,3-disubstituted-1,2,4-triazoles. It was noticed that analogous *N*-acyl-2,6-



Scheme 52 Synthesis of 1,2,4-triazole derivatives containing *C*-glycopyranosyl.



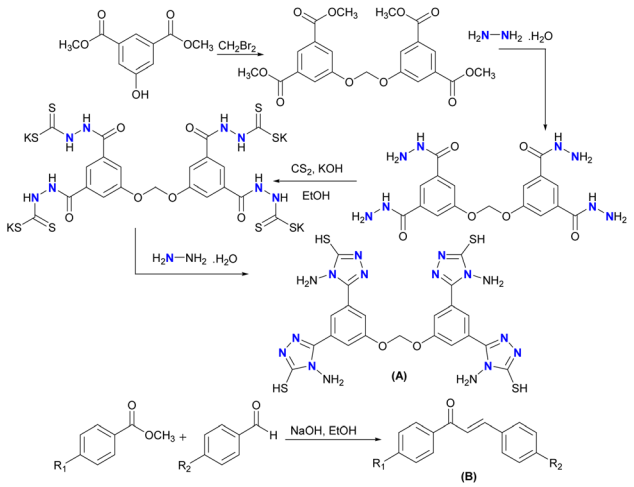
Scheme 53 Synthesis of 1,2,4-triazoles from simple primary amines or aniline derivatives.

anhydro-heptonamides failed to give the triazoles with hydrazine (Scheme 52).[122]

Scott M. Hutchinson and co-workers developed an alternative two-step synthesis involving the conversion of a primary amine or aniline derivative to the corresponding 4-substituted 1,2,4-triazole. In this method, primary amines or aniline derivatives react with a hydrazine derivate of ((dimethylamino) methylene)-*N*,*N*-dimethylformohydrazonamide under catalytic hydrogenation produces 4-substituted 1,2,4-triazoles, which on further reaction with diaryliodonium salts *via* copper-catalyzed arylation form 1,4-diaryl- and 1-aryl-4-alkyl-substituted 1,2,4-triazolium salts. These salts are convenient air-stable carbenes and can be used as both organo-catalysts or ligands for the preparation of transition metal complexes (Scheme 53).[123]

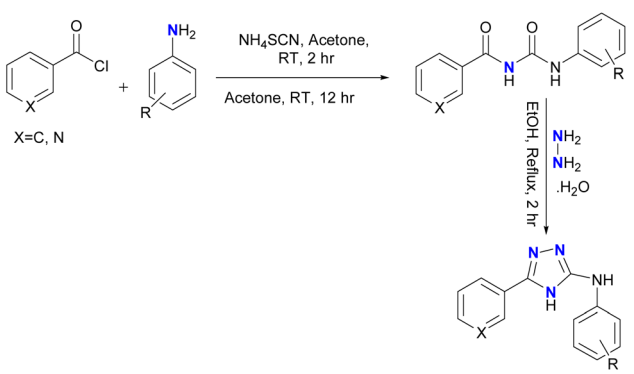
A library of 5-aryl-3-amino-1,2,4-triazole derivatives was synthesised by reacting aryl acid chlorides with anilines in the presence of ammonium thiocyanate and acetone, followed by treatment with hydrazine hydrate in the presence of ethyl alcohol (EtOH) under reflux for 2 h. The reaction follows simple steps and can synthesise a library of compounds with anticancer activity against a panel of cancer cell lines using XTT assay, and also antiangiogenic activity. This method was proposed by Oleksandr Grytsai and co-workers in 2020 (Scheme 54).[124]

A giant molecule, 3,3′,3″,3‴-[methylenebis(oxybenzene-5,1,3-triyl)]tetrakis(6,8-diaryl[1,2,4]triazolo[3,4-b][1,3,4] thiadiazep-ines), was prepared from dimethyl 4-hydroxyisophthalate and dibromomethane as the starting materials by A. N. Ayyash in 2021. Tetramethyl 5,5′-[methylenebis(oxy)] di(benzene-1,3-dicarboxylate) was formed upon the reaction between the starting materials, which was subsequently treated with an excess of hydrazine hydrate. The resulting intermediate was then converted to the tetrakis(1,2,4-triazolyl) derivative in the presence of ethanolic potassium hydroxide (KOH), carbon disulfide (CS_2), and hydrazine hydrate *via* an intramolecular cyclization mechanism. In the final stage, the obtained tetrakis 1,2,4-triazolyl derivative was treated with substituted chalcogens to afford the desired 1,2,4-triazole derivatives. This synthetic strategy highlights the efficiency and versatility of 1,2,4-triazole frameworks in the construction of complex polycyclic systems. The incorporation of chalcogen substituents significantly broadens the structural diversity and potential functional properties of the resulting molecules. This approach provides additional insight into the expanding scope of 1,2,4-triazole chemistry and its emerging role in the development of advanced heterocyclic scaffolds with promising biological and material applications (Scheme 55).[125]

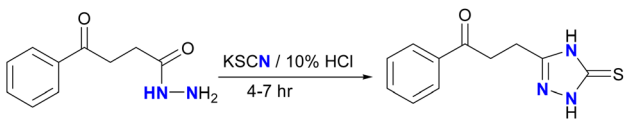


Scheme 55 Synthesis of 1,2,4-triazoles from dimethyl-4-hydroxyisophthalate and dibromomethane.

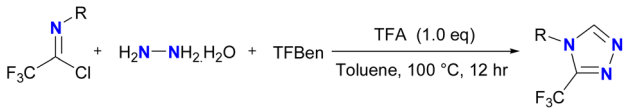
Ameen Ali Abu-Hashem reported a simple method for the synthesis of 1,2,4-triazole derivatives from 4-oxo-4-phenylbutanehydrazide with potassium thiocyanate under neat conditions. The formed 1,2,4-triazole derivatives were tested for their *in vitro* antitumor activities. The compounds displayed activity against several types of cancer cell lines (Scheme 56).[126]



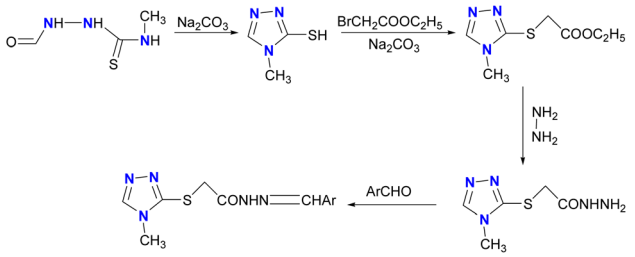
Scheme 54 Synthesis of 1,2,4-triazoles from primary amines and aryl acid chlorides.



Scheme 56 Synthesis of 1,2,4-triazoles from 4-oxo-4-phenylbutanehydrazide.



Scheme 57 Synthesis of 3-trifluoromethyl-1,2,4-triazoles under metal-free conditions.



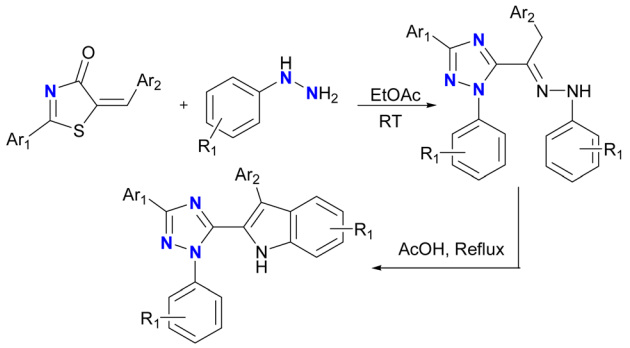
Scheme 58 Synthesis of 1,2,4-triazoles from 1-formyl-4-methyl-3-thiosemicarbazide.

A simple and metal-free approach for the construction of pharmaceutically valuable 3 trifluoromethyl-1,2,4-triazoles was developed by Binjie Wang and co-authors in 2022. This method proceeds *via* the reaction between readily available trifluoroacetimidoyl chlorides, hydrazine hydrate and benzene-1,3,5-triyl triformate (TFBen) as the starting materials, offering triazole scaffolds in moderate to good yields with broad substrate scope, high efficiency, and scalability. Further studies toward the synthesis of functionalized heterocycles in a simple manner are underway (Scheme 57).[127]

A simple method for the synthesis of 1,2,4-triazole derivatives using 1-formyl-4-methyl-3-thiosemicarbazide as the starting material was described by P. N. Shinde and co-workers in 2023. Triazole Schiff bases were synthesized *via* the reaction of hydrazide with various aromatic aldehydes in glacial acetic acid medium. The newly synthesised compounds were found to have excellent antibacterial and antifungal activity against various bacterial pathogens such as *S. aureus* and *E. coli* and fungal species *C. albicans* and *A. niger* (Scheme 58).[128]

An efficient metal-free approach for the synthesis of various 1,2,4-triazoles linked by a benzyl bridge was reported by Mariswamy K. Sreelekha and co-authors in 2024. This method proceeds *via* the one-pot reaction of hydroxy coumarin, *trans-b*-nitrostyrene, and aldehyde hydrazone in the presence of sodium carbonate. The salient features of this protocol are a broad substrate scope, mild reaction conditions, and metal and ligand-/additive-free approach. In addition to 1,2,4-triazoles, they also synthesised various 1,3-dione derivatives using the same method. Subsequent investigations to expand the scope of this strategy to other substrates are underway (Scheme 59).[129]

The simple and catalyst-free synthesis of hydrazone-substituted 1,2,4 triazoles *via* ring opening/intramolecular cyclization of arylidene thiazolone by aryl/alkyl-hydrazine was reported by Akanksha Kumari and co-authors in 2025. The reaction proceeds *via* molecular editing of arylidene thiazolone with aryl/alkyl hydrazines. Furthermore, the direct one-pot synthesis of indole-substituted 1,2,4-triazole expands its structural diversity, showcasing broad substrate applicability (Scheme 60).[130]

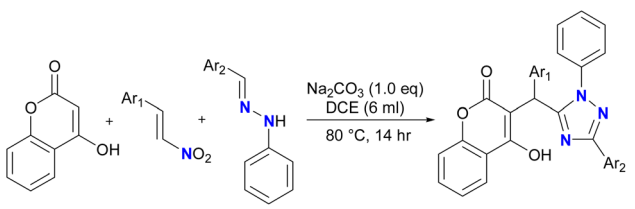


Scheme 60 Synthesis of hydrazone-substituted 1,2,4-triazoles *via* ring opening/intramolecular cyclization.

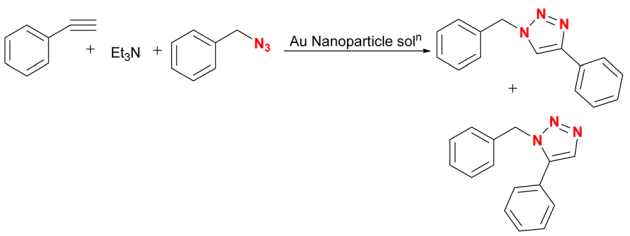
3.3 Miscellaneous methods

3.3.1 Nanoparticle-based catalysts. A very interesting and novel method for the synthesis of 1,2,3-triazole derivatives was developed using gold (Au) nanoparticles. Gold nanocubes, octahedra, and rhombic dodecahedra were used as the medium for the synthesis of triazoles. Among the nanoparticles, rhombic dodecahedra gave 100% regioselective 1,4-triazoles. The product yield was increased by decreasing the particle size. The reaction proceeds with the formation of an Au–acetylide intermediate, in which phenylacetylene binds to the gold (Au) {110} surface through the terminal-binding mode from terminal alkynes and azides, resulting in the exclusive formation of 1,4-disubstituted 1,2,3-triazoles (Scheme 61).[131]

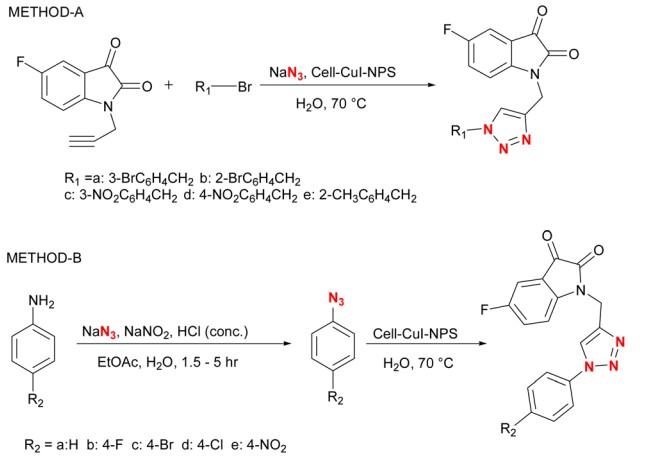
An environmentally friendly heterogeneous catalyst, Cell-CuI-NPs, was used for the synthesis of biologically active 1-((1-aryl)-1*H*-1,2,3-triazol-4-yl)methyl-5-fluoroindoline-2,3-diones *via* copper-catalysed azide alkyne cycloaddition (CuAAC) click reaction of 5-fluoro-(1-prop-2-ynyl)indoline-2,3-dione, an alkyne with various organic azides in aqueous medium. Based on the different starting materials used, this scheme is divided into two parts (A and B), where both starting materials undergo click reaction to produce substituted 1,2,3-triazoles (Scheme 62).[132]



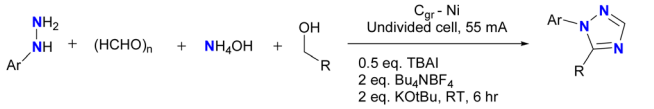
Scheme 59 Synthesis of 1,2,4-triazoles *via* one-pot reaction of hydroxy coumarin, *trans-b*-nitrostyrene, and aldehyde hydrazone.



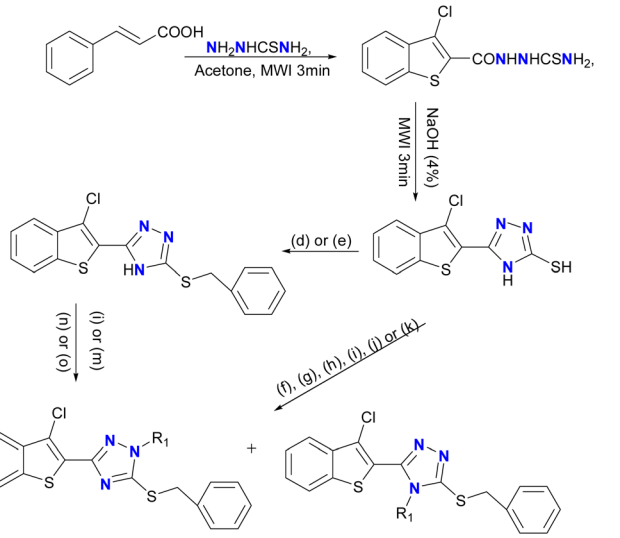
Scheme 61 Synthesis of 1,2,3-triazoles using gold nanoparticles.



Scheme 62 Synthesis of 1,2,3-triazoles using heterogeneous catalyst Cell-CuI-NPs.



Scheme 63 Synthesis of 1,2,4-triazoles *via* the electrochemical method.



Scheme 64 Synthesis of 1,2,4-triazoles using microwave irradiation (MWI). (d) $ClCH_2Ph$, NEt_3, EtOH, Reflux 1 h; (e) $ClCH_2Ph$, NEt_3, EtOH, MWI 1.5 min; (f) $ClCH_2Ph$, KOH, DMF, reflux 4 h; (g) $ClCH_2Ph$, KOH, DMF, MWI 3 min; (h) $ClCH_2Ph$, NaH, DMF, st. 4 h; (i) $ClCH_2Ph$, NaH, DMF, MWI 3 min; (j) $ClCH_2Ph$, K_2CO_3, DMF, st. 5 h; (k) $ClCH_2Ph$, K_2CO_3, DMF, MWI 3.5 min; (l) $ClCH_2Ph$, KOH, DMF, Reflux 3 h; (m) $ClCH_2Ph$, KOH, DMF, MWI 2.5 min; (n) $CH_2{=}CHCH_2Br$, K_2CO_3, DMF, st. 4 h; and (o) $CH_2{=}CHCH_2Br$, K_2CO_3, DMF, MWI 2 min.

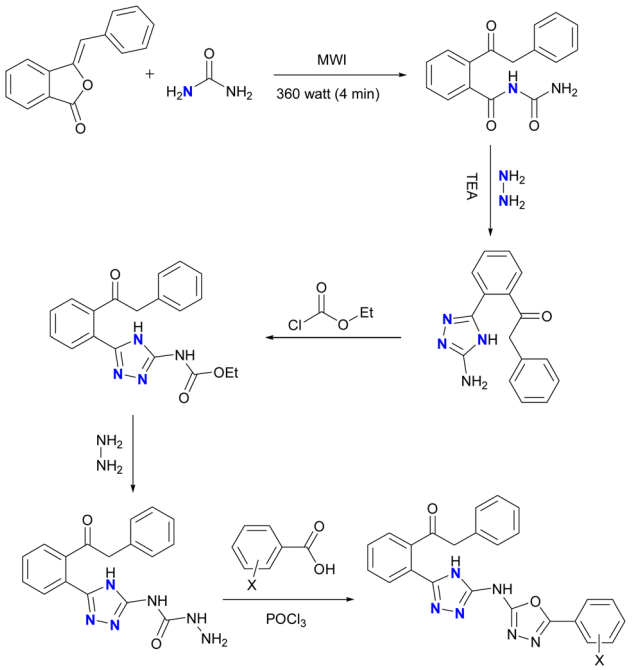
An electrochemical method was developed by Na Yang and Gaoqing Yuan for the synthesis 1,5-disubstituted and 1-aryl-1,2,4-triazoles from paraformaldehyde, aryl hydrazines, ammonium acetate and alcohols. In this case, alcohols act as both the solvent and starting material and ammonium acetate (CH_3COONH_4) is used as the nitrogen source for the construction of triazoles. This method is carried out at room temperature under metal- and catalyst-free conditions. The reaction mechanism involves the generation of free radicals (Scheme 63).[133]

3.3.2 Microwave-assisted synthesis. In 2006, E. S. H. El Ashry and co-workers developed an efficient method for the synthesis of 1,2,4-triazole derivatives under microwave irradiation (MWI) *via* intramolecular cyclization of carbonyl thiosemicarbazides in good yield. This method allows the preparation of a library of 1,2,4-triazole derivatives with almost similar reagents and reaction conditions. The protocol offers a rapid, clean, and high-yielding alternative to conventional heating techniques, demonstrating the advantages of microwave-assisted synthesis in heterocyclic chemistry (Scheme 64).[134]

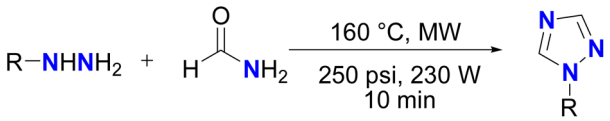
A typical method for the synthesis of 1,2,4-triazole derivatives containing 1,3,4-oxadiazoles was developed by Shaymaa K. Younis in 2011 from 3-benzylidene phthalide as the starting precursor. 3-Benzylidene phthalide was reacted with urea under 360 W microwave irradiation and dry conditions to afford the corresponding 1-(2-(α-phenylacetyl)benzoyl)urea, followed by cycloaddition reaction with 80% of hydrazine hydrate to give 1-(2-(5-amino-4*H*-1,2,4-triazol-3-yl)phenyl)-2-phenylethanone, which on further treatment with ethyl chloroformate forms ethyl-5-(2-(α-phenylacetyl)phenyl)-4*H*-1,2,4-triazol-3-yl-carbamate. Subsequently, upon reaction with 80% hydrazine hydrate, it forms 4-(5-(2-(α-phenylacetyl)phenyl)-4*H*-1,2,4-triazol-3-yl) semicarbazide under mild conditions. The so-formed 4-(5-(2-(α-phenylacetyl)phenyl)-4*H*-1,2,4-triazol-3-yl) semicarbazide finally reacts with various substituted benzoic acids in the presence of phosphorous oxychloride to form 2-phenyl-1-(2-(5-(5-aryl-1,3,4-oxadiazol-2-yl-amino)-4*H*-1,2,4-triazole-3-yl)phenyl)ethenone (Scheme 65).[135]

The microwave-assisted synthesis of substituted 1,2,4-triazoles from hydrazines and formamide was developed under metal-free and catalyst-free conditions. This reported method proceeds smoothly in the absence of a catalyst and requires mild reaction conditions. The use of microwave irradiation significantly reduces the reaction time and improves the overall yield compared to conventional heating methods. Moreover, this eco-friendly and efficient protocol aligns well with green chemistry principles, making it a sustainable alternative for the synthesis of triazoles (Scheme 66).[136]

3.3.3 Synthesis of bifunctional triazoles. A typical method for the synthesis of biologically active compounds containing both 1,2,3-triazole and 1,2,4-triazole moieties was developed. Compounds containing both 1,2,3-triazole and 1,2,4-triazole functional groups were synthesized by Yan Zou and co-workers in 2012. In this method, a series of 1-(1*H*-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-substituted-2-propanols derivatives were prepared *via* copper-catalyzed azide–alkyne cycloaddition (CuAAC) reaction. The prepared triazole derivatives are analogues of antifungal derivatives of triazole (specifically fluconazole), which showed tremendous antifungal activity against eight human pathogenic fungi, as confirmed by



Scheme 65 Synthesis of 1,2,4-triazoles from 3-benzylidene phthalide.



Scheme 66 Microwave-assisted synthesis of 1,2,4-triazoles.

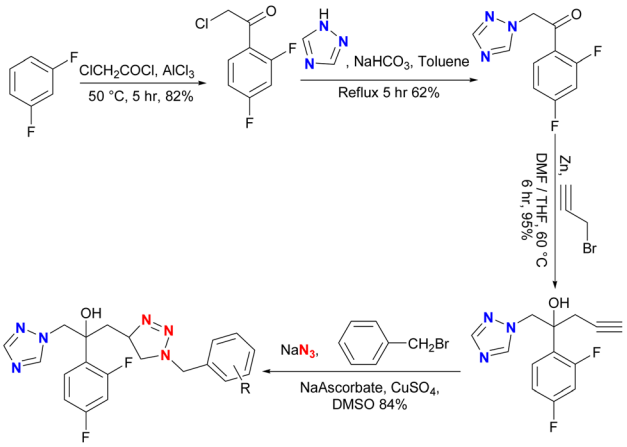
computational docking experiments on the molecules to study the active site of the cytochrome P450 14a demethylase (CYP51). This dual-triazole framework significantly enhanced the biological efficacy compared to the single triazole analogues. This study demonstrated the potential of combining 1,2,3- and 1,2,4-triazole motifs to design multifunctional therapeutic agents with improved target specificity (Scheme 67).[137]

4 Comparative analysis of synthetic methodologies for triazoles

The synthesis of 1,2,3- and 1,2,4-triazoles has undergone significant evolution from classical condensation-based reactions to highly efficient and sustainable catalytic systems. A comparative evaluation of the reported methodologies demonstrates distinct mechanistic preferences, catalytic profiles, and environmental implications between these two frameworks.

4.1 Synthetic methodologies for 1,2,3-triazoles

Among the various reported routes, copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC), originally proposed by Huisgen, and later developed by Meldal and Sharpless, remains the most prominent and regioselective approach for the preparation of 1,4-disubstituted-1,2,3-triazoles under mild aqueous or solvent-



Scheme 67 Miscellaneous synthesis of 1,2,3-and 1,2,4-triazole derivatives.

free conditions (Scheme 18, ref. 88). Ruthenium-catalyzed azide–alkyne cycloaddition (RuAAC) expands this chemistry toward 1,5-disubstituted analogues through transition metal-mediated dipolar cycloadditions (Scheme 2, ref. 46–48). Metal-free strategies have attracted wide attention owing to their environmental compatibility and simple work-up, including amine-catalyzed, ionic-liquid-promoted, vinyl sulfone and organocatalytic systems, which provide high regioselectivity without the need for transition metals (Scheme 28, ref. 98). The advent of heterogeneous catalysis, notably Cell–CuI NPs, polymer-supported Cu–azide nanoparticles (CANPs) and Cu-on-charcoal systems, has enhanced the recyclability, stability, and recovery of catalysts, marking a shift toward operationally benign click processes (Schemes 17–19, 32, 62, ref. 87–89, 102, and 132). Nanoparticle-assisted catalysis, employing Au, Ag and $Er(OTf)_3$ systems, further improved the yield and selectivity *via* enhanced surface activity and mild reaction conditions (Scheme 15, ref. 85). Green and sustainable developments, such as microwave-assisted protocols, ionic-liquid-mediated CuAAC reactions, and biodegradable solvent systems (Cyrene™), have shortened the reaction times and reduced waste production, while maintaining high product yields (Scheme 22, ref. 92).

4.2 Synthetic methodologies for 1,2,4-triazoles

The construction of 1,2,4-triazoles primarily proceeds through cyclization reactions of hydrazines, hydrazides, thiosemicarbazides, amidines, and related precursors. The pioneering Ainsworth oxidation method, involving thiosemicarbazide and formic acid, remains a fundamental historical route (Scheme 40, ref. 110), while El Ashry's microwave-assisted cyclization significantly advanced the field by achieving rapid intramolecular ring closure of carbonyl thiosemicarbazides in high yield (Scheme 64, ref. 134). Recent methodologies highlight the use of Cu(II)- and Zn(II)-mediated oxidative couplings (Scheme 34, ref. 104) and one-pot metal-free reactions *via* cyanoimidation, amidination, or aldehyde condensation, providing clean and high-yielding protocols. Microwave-assisted and electrochemical systems further

enhance the efficiency and sustainability by reducing the energy input and eliminating hazardous reagents (Schemes 63 and 66, ref. 133 and **136**), respectively. Additionally, advanced protocols integrating trifluoromethylation (Scheme 57, ref. 127) and glycopyranosyl-linked (Scheme 52, ref. 122), and benzyl-bridged frameworks (Scheme 59, ref. 129) demonstrate the synthetic versatility and structural diversity achievable through modern 1,2,4-triazole chemistry.

4.3 Comparative evaluation and outlook

Mechanistically, 1,2,3-triazoles are predominantly formed *via* [3 + 2] cycloadditions between azides and alkynes, an archetypal click reaction, offering modularity, regioselectivity, and high atom economy. In contrast, 1,2,4-triazoles arise mainly through condensation or oxidative coupling of nitrogen-rich substrates, reflecting a more classical heterocyclic assembly pathway. Although copper-catalyzed azide–alkyne cycloaddition (CuAAC) continues to represent the benchmark for regioselectivity and synthetic simplicity, the integration of microwave irradiation, electrochemical systems, and ionic-liquid-based recyclable media marks a pivotal transition toward greener, scalable, and economically viable triazole synthesis. The convergence of mechanistic insight, catalytic innovation, and sustainable chemistry now positions triazoles as exemplary frameworks for next-generation heterocyclic synthesis.

5 Conclusions

In this review, we have summarized the Huisgen cycloaddition reaction as an excellent approach for the synthesis of 1,2,3- and 1,2,4-triazoles from various azide and acetylene sources. This review outlines the literature related to different synthetic and modern routes for the target molecules with triazole as the main constituent. The approaches mentioned here are helpful for researchers and practitioners. The triazole compound, which contains three nitrogen and two carbon atoms, possesses a high electron density and provides scaffolds with a diverse range of potential applications in real life. Based on this, researchers can develop more advanced, economical, and modern approaches for the synthesis of triazoles. In addition, the exploration of computational and mechanistic aspects has significantly enhanced the understanding of the reaction pathways, regioselectivity, and catalytic efficiency, paving the way for the rational design of innovative reaction systems. Recent advancements in green and sustainable chemistry have further contributed to the development of eco-friendly, energy-efficient, and high-yielding protocols. Overall, this review provides a comprehensive foundation for future research aimed at designing novel triazole-based systems with promising applications in pharmaceuticals, materials science, and catalysis.

Author contributions

RT conceived and designed the study. MA wrote the main manuscript. All the authors proofread and reviewed the manuscript.

Conflicts of interest

The authors declare that they have no competing interests.

Data availability

No primary research results, software or code have been included, and no new data were generated or analysed as part of this review.

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