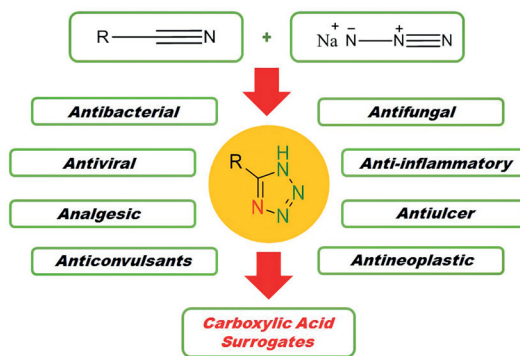# Recent Advances in the Synthesis of 5-Substituted 1*H*-Tetrazoles: A Complete Survey (2013–2018)

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Dedicated in the memory of my beloved brother, the late Mr. Sushil Kumar Awasthi.

Abstract Tetrazoles are synthetic organic heterocyclic compounds comprising of high nitrogen content among stable heterocycles. Tetrazoles, chiefly 5-substituted 1*H*-tetrazoles have been used as a bioisosteric replacement for carboxylic acids in medicinal chemistry. Various clinical drugs, including losartan, cefazolin, and alfentanil, contain the tetrazole moiety. There have been significant developments in the synthesis of 5-substituted 1*H*-tetrazoles. Researchers are still working to develop more efficient and ecofriendly methods for their synthesis. In this review, we provide a comprehensive discussion of the recent advancements in the field of synthesis of 5-substituted 1*H*-tetrazoles.

1 Introduction

Tetrazoles are synthetic organic heterocyclic compounds made up of a five-membered ring with four nitrogen atoms and one carbon atom. They have a high nitrogen content amongst the stable heterocycles. On the basis of the number of substituents, tetrazoles are divided into four categories (Figure 1): (i) parent tetrazoles (simplest), (ii) monosubstituted tetrazoles (1-, 2-, or 5-substituted), (iii) disubstituted tetrazoles (1,5- or 2,5-disubstituted), and (iv) trisubstituted tetrazolium salts (1,3,5-, 1,4,5-, or 2,3,5-trisubstituted, where X⁻ is any anion like Cl⁻, ClO₄⁻, etc.).
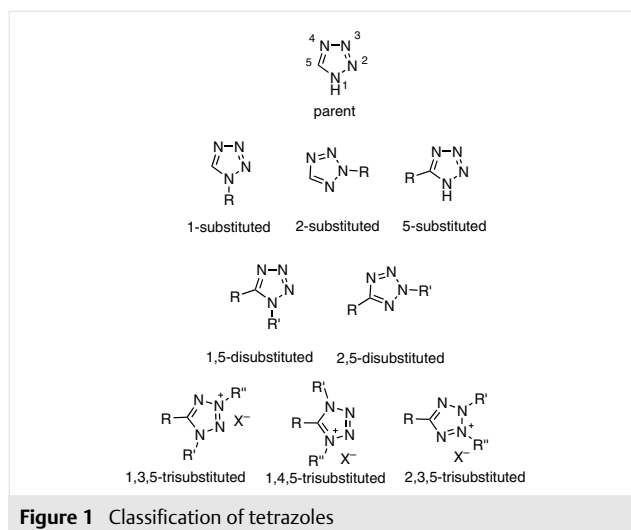

Figure 1 Classification of tetrazoles

Tetrazole was first synthesized and characterized by J. A. Bladin in 1885,[1,2] at the University of Uppsala. Tetrazoles are stable over a wide pH range and they are also stable to various oxidizing and reducing agents.[3] They play an important role in coordination chemistry as ligands,[4] in material science as explosives,[5] in photography,[6] and act as carboxylic acid surrogates in medicinal chemistry.[7] They act as versatile pharmacophores in medicinal chemistry due to the presence of multiple nitrogen atoms in their structure. Tetrazole ring containing drugs belong to antibacterial,[8] antifungal,[9] antiviral,[10,11] analgesic,[12,13] anti-inflammatory,[14,15] anticonvulsants,[16] anti-allergic,[17] antiulcer,[18] and antineoplastic[19] categories.

Some biphenyl-substituted tetrazoles have found application in the synthesis of certain antihypertensive drugs like losartan, irbesartan, valsartan, cefazolin, and azosemide (Figure 2) which are used to treat high blood

pressure.[20] Tetrazoles have also been used in the treatment of cancer[21] and AIDS.[22] Tetrazole derivatives are used agriculture as plant growth regulators and as herbicides and fungicides for crop protection.[4,23] They also act as intermediates that are used in the synthesis of some complex heterocyclic compounds through various rearrangements.[24]

5-Substituted 1*H*-tetrazoles are the most important and interesting category of tetrazoles due to their extensive applications in the field of medicinal chemistry. Hence, in this review our primary emphasis will be on the recent advancements in the synthesis of 5-substituted 1*H*-tetrazoles.

This review summarizes the numerous synthetic approaches that have been employed for the synthesis of 5-substituted 1*H*-tetrazoles in the years 2013–2018. A review of the synthesis of 5-substituted 1*H*-tetrazoles until 2012 is available.[26a]

2 The Role of 5-Substituted 1*H*-Tetrazoles in Medicinal Chemistry

5-Substituted 1*H*-tetrazoles are frequently used in medicinal chemistry as carboxylic acid surrogates, or more appropriately as their bioisosteric replacement.[25a] Although both these functional groups differ from each other in terms of their structure, they still display similar biological activity due to closely related physiochemical properties.[25b]

5-Substituted 1*H*-tetrazoles containing a free N–H bond exist in two tautomeric forms: 1*H*- and 2*H*-tautomers in approximately 1:1 ratio (Scheme 1).[26a] One important as-

pect that determines the bioisosteric interchangeability is the correspondence between the pK_a values of 5-substituted 1*H*-tetrazoles and carboxylic acids (Table 1).[26b,27]
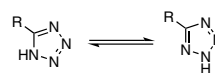
Scheme 1 Two tautomeric forms of 5-substituted 1*H*-tetrazoles

Table 1 Comparison between the Acidities of Carboxylic Acids and Their Corresponding 5-Substituted 1*H*-Tetrazoles

Substituents	pKa (carboxylic acid)	pKa (tetrazole)
H	3.77	4.70
CH$_3$	4.76	5.50
Et	4.88	5.59
CH$_2$CH$_2$	4.19, 5.48	4.42, 5.74
Ph	4.21	4.83

Tetrazoles, like their carboxylic acid counterparts, have a planar structure and they are ionized at physiological pH values. However, it has been shown that tetrazole anions are 10 times more lipophilic than carboxylate anions.[26a] The higher lipophilicity of tetrazole anions can account for its pharmacokinetics, that is, tetrazole anions can display higher membrane permeability. Larsen, Liljebris, and co-workers[28] reported that introduction of the lipophilic tetra-

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Biographical Sketches

Rupali Mittal received her undergraduate education from University of Delhi, India in 2014. Later, she completed her post-graduation from the De- partment of Chemistry, University of Delhi, India in 2016. She is currently pursuing her Ph.D. at Department of Chemistry, University of Delhi under the su- pervision of Prof. S. K. Awasthi. She has been working on various applications of sulfonated reduced graphene oxide in synthetic organic chemistry.
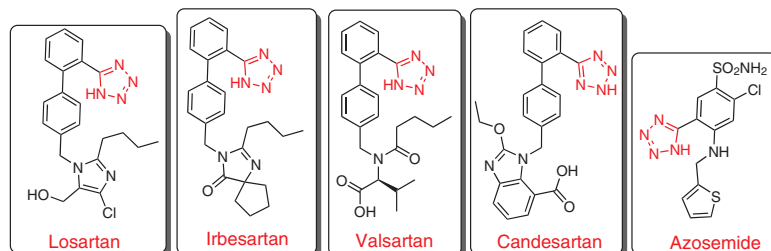
Dr. Satish Kumar Awasthi was awarded a D.Phil. in 1991 from Allahabad University, UP, India. He received a National Research Associateship from DBT, Government of India to work at the Molecular Biophysics Unit, IISc, Bangalore, India. He is a recipient of several awards including the TIT-UNICEF Fellowship Award, Tokyo, Japan, INSA visit- ing scientist in Germany, ICMR-Biomedical Young Scientist Award at the University of Co- penhagen, Denmark and The Commonwealth Academic fellowship award at the Royal Vet- erinary College, University of London, London. Dr. Awasthi has been working in diversified are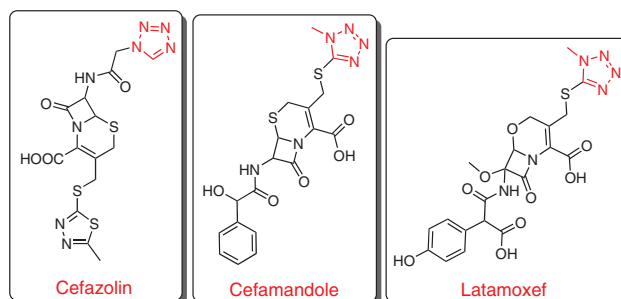as ranging from peptide chemistry to drug delivery. More specifically, he has been working on the antisense properties of peptide nucleic acids (PNAs), the design and synthesis of small molecules for anti- bacterial and antimalarial studies, and the X-ray crystal structure analysis of small mole- cules.

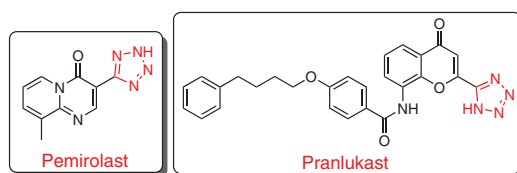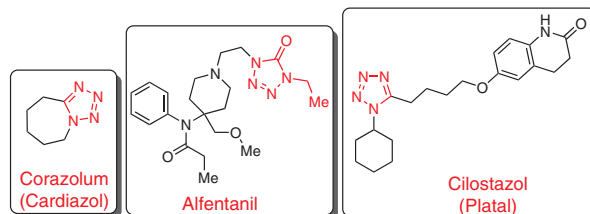**Figure 2** Marketed drugs containing tetrazole moiety

zole moiety into a series of PTB1B inhibitors resulted in significantly higher Caco-2 cell permeability as compared to the corresponding carboxylate analogues. When talking in terms of pharmacodynamics, the effect of the replacement of a carboxylic acid with a 5-substituted 1*H*-tetrazole is intricate. It cannot be accurately predicted whether the pharmacodynamics will increase, decrease, or disappear completely.[29] Depending upon the electron distribution within a receptor site, the negative charge delocalization in the tetrazole ring can either enhance or reduce interaction with a particular receptor.[30] The larger size of the tetrazole ring

as compared to the carboxylate anion may reduce its binding affinity at the active site. This may either be a result of steric hindrance or inappropriate orientation of functional groups of the active site.[31] The interaction of the tetrazole ring (vs. the carboxylate anion) with a receptor site may be enhanced because of the ability of all its nitrogen atoms to act as hydrogen bond acceptors. The chief advantage of 5-substituted 1*H*-tetrazoles over carboxylic acids is that they are resistant to numerous biological metabolic degradations. The main metabolic transformation observed for 5-

substituted 1*H*-tetrazoles involves glucuronidation of one of its nitrogen atoms, where both its tautomers can serve as substrates.[26a]

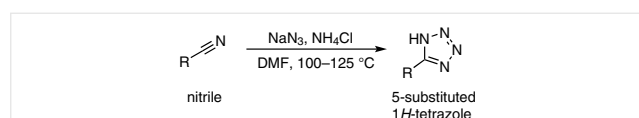## 3   Synthesis of 5-Substituted 1*H*-Tetrazoles

Before the [3+2]-cycloaddition reaction, one of the first extensively used methods for the synthesis of 5-substituted 1*H*-tetrazoles consisted of the diazotization of amidrazones. These amidrazones were prepared from imidates and hydrazine. In this method, an imidoyl azide was formed prior to the formation of a 5-substituted 1*H*-tetrazole (Scheme 2).[32]
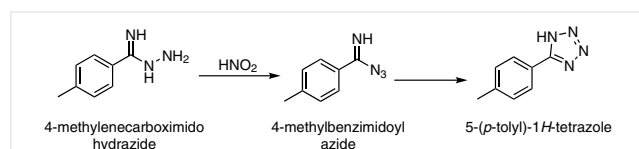
Scheme 2   Synthesis of 5-substituted 1*H*-tetrazole from amidrazones

In 1901 Hantzsch and co-workers reported the synthesis of 5-amino-1*H*-tetrazole from cyanamide and hydrazoic acid (azoimide).[33] This route involving the [3+2] cycloaddition of an azide with a nitrile has now become the conventional method employed for the synthesis of 5-substituted 1*H*-tetrazoles.[33] Until the 1950s, hydrazoic acid and hydrogen cyanide were used as major reactants for the preparation of tetrazoles. These reactants are problematic, for example hydrazoic acid is highly volatile, toxic and explosive.[34a] Moreover, this method suffers from various other drawbacks like moisture-sensitive reaction conditions and the use of strong Lewis acids.[34b] This led to increased efforts towards modifying the methods for the synthesis of 5-substituted 1*H*-tetrazoles.

In 1958, Finnegan and co-workers[35] reported their fundamental work with an improved procedure for the preparation of 5-substituted 1*H*-tetrazoles from nitriles using inorganic sodium azide and ammonium chloride in DMF (Scheme 3).

Scheme 3   Synthesis of 5-substituted 1*H*-tetrazoles from nitriles using sodium azide and ammonium chloride

Subsequently, effort has been put into designing newer synthesis protocols that are safer, decrease reaction time, and increase product yields. In order to reduce reaction time, microwave (MW) irradiation has been employed. Over the years, the use of a variety of catalysts with varying

reaction conditions has been explored; for example, Lewis acids (such as $BF_3 \cdot OEt_2$,[36] $ZnBr_2$,[37] etc.), a stoichiometric amount of inorganic salts,[37,38] metal complexes,[39] and ionic liquids[40] have all been used as catalysts. However, these homogeneous catalysts have shortcomings like tedious separation procedures and poor recovery and recyclability. Thus, to overcome these drawbacks, heterogeneous catalysts like nanocrystalline ZnO,[41a] $CuFe_2O_4$ nanoparticles (NPs),[41b] mesoporous ZnS,[41c] CoY zeolite,[41d] $Fe_3O_4@SiO_2$,[41e] Ag NPs,[41f] Au NPs,[41g] graphene,[41h] graphene oxide/ZnO nanocomposites,[41i] Pt NPs@rGO,[41j] $SnCl_2$-nano-SiO_2,[41k] etc. have been employed in the synthesis of 5-substituted 1*H*-tetrazoles. The efforts towards developing safer and efficient synthesis protocols are still underway.

This section will further elaborate upon various synthetic methods that have been used in the period 2013–2018 for the synthesis of 5-substituted 1*H*-tetrazoles (Figure 3).
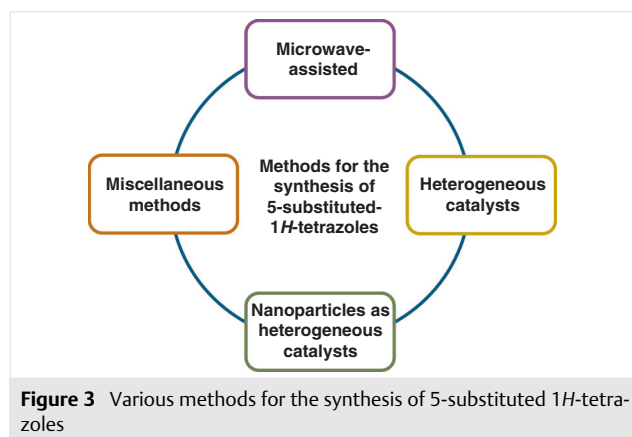

Figure 3   Various methods for the synthesis of 5-substituted 1*H*-tetrazoles

3.1   Microwave-Assisted Synthesis

The synthesis of 5-substituted 1*H*-tetrazoles is challenged with long reaction times. Microwave (MW) irradiation has been employed to overcome this drawback. The first work consisting of microwave-assisted organic reactions was published in 1986. In spite of high cost of dedicated microwave apparatus, it is still quite popular. Microwave irradiation is believed to be superior to conventional heating in terms of reduced reaction time, enhanced yields, and purity of reactions.[42]

MW irradiation was employed by Harusawa and co-workers[43] for the transformation of inactive nitriles into 5-substituted 1*H*-tetrazoles in DMF (Scheme 4a). They compared MW-assisted synthesis with conventional heating. The reaction of 3-phenylpropionitrile with sodium azide and triethylamine hydrochloride in DMF under MW irradiation gave 5-phenethyl-1*H*-tetrazole in 69% yield after 2 hours whereas under conventional heating the reaction re-

Scheme 4 Examples of the microwave-assisted synthesis of 5-substituted 1*H*-tetrazoles
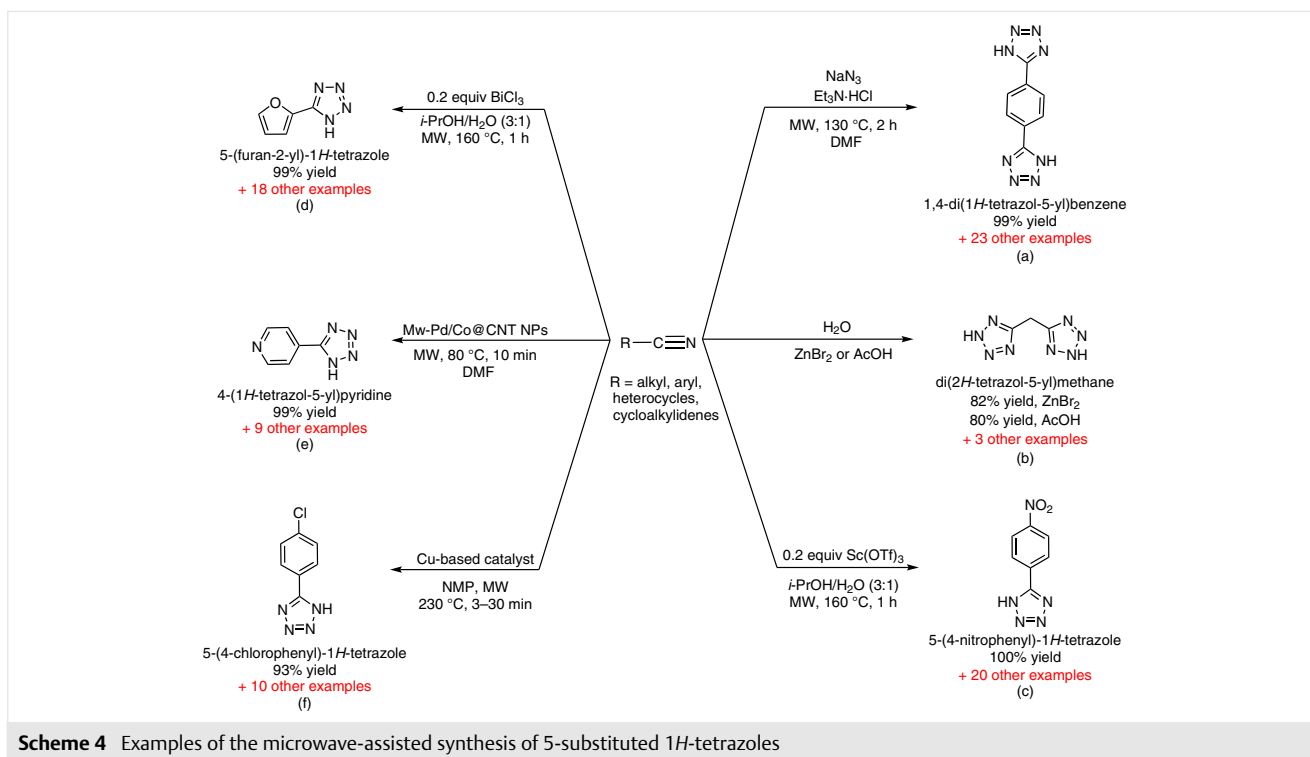
quired 130 °C for 40 hours to give a yield of 79%. A variety of 5-substituted 1*H*-tetrazoles were synthesized by this microwave route in good to excellent yields (63–99%).

An environmentally benign protocol for the synthesis of 5-substituted 1*H*-tetrazoles by the [3+2]-cycloaddition reaction of nitrile and azide derivatives in water under MW irradiation employing ZnBr$_2$ or AcOH as a catalyst was introduced by El-Remaily and Mohamed (Scheme 4b).[44] Four examples of 5-substituted 1*H*-tetrazoles were obtained in good yields (80–85%) in 10–15 minutes; of these, three showed *in vitro* antibacterial activity against *Bacillus cereus*, *Bacillus subtilis*, *Escherichia coli* and *Pseudomonas aeruginosa* while only one showed antifungal activity against *Penicillium purpurogenum*, *Aspergillus flavus* and *Trichothecium rosium*. It was inferred that the 5-substituted 1*H*-tetrazole having a symmetrical structure displayed highest inhibitory action.

Coca and co-workers[45] prepared 5-substituted 1*H*-tetrazoles in water or *i*-PrOH/water mixtures using scandium triflate as a catalyst under MW irradiation (Scheme 4c). The [3+2]-cycloaddition reaction between nitrile derivatives (aryl, aliphatic, and vinyl nitriles) and sodium azide under the optimized conditions of *i*-PrOH/water (3:1) under MW irradiation at 160 °C for 1 hour gave the corresponding 5-substituted tetrazoles in 25–100% yields. For example, 4-nitrobenzonitrile gave 5-(4-cyanophenyl)-1*H*-triazole in 100% yield, while 2-(2-methoxyphenyl)acetonitrile gave 5-(2-methoxybenzyl)-1*H*-triazole in a low 25% yield. Coca and co-workers[46] also used bismuth chloride as a catalyst

under same reaction conditions for the synthesis of 5-substituted 1*H*-tetrazoles with yields of up to 99% (Scheme 4d); furan-2-carbonitrile gave 5-(2-furyl)-1*H*-tetrazole in 99% yield.

The use of a heterogeneous catalyst when using MW irradiation for the synthesis of 5-substituted 1*H*-tetrazoles give this procedure an edge over other methods by making separation easier and producing higher yields in less reaction time. In view of this, Kaya, Sen, and co-workers[47] reported the MW-assisted synthesis of 5-substituted 1*H*-tetrazoles catalyzed by monodisperse Pd/Co nanoparticles (Mw-Pd/Co@CNT NPs) decorated multi-walled carbon nanotubes (Scheme 4e). The heterogeneous catalyst was found to be highly crystalline, monodisperse, and colloidally stable. The reaction was completed in very short time (ca. 10 min) and gave 5-substituted 1*H*-triazoles in excellent yields (90–99%). A plausible mechanism for the synthesis is shown in Scheme 5. This procedure was highly efficient and environmentally benign with simple methodology and easy workup.

A MW-assisted protocol for the synthesis of 5-substituted 1*H*-tetrazoles via [3+2]-cycloaddition reaction between various nitrile derivatives and sodium azide in the presence of a heterogeneous Cu(II) catalyst using *N*-methyl-2-pyrrolidone as the solvent was reported by Rohe and co-workers (Scheme 4f).[48] Mechanistically it is proposed that the Cu(II) species activates the nitrile group, and this is followed by [3+2] cycloaddition of this activated nitrile with sodium azide (Scheme 6). The products were obtained in high
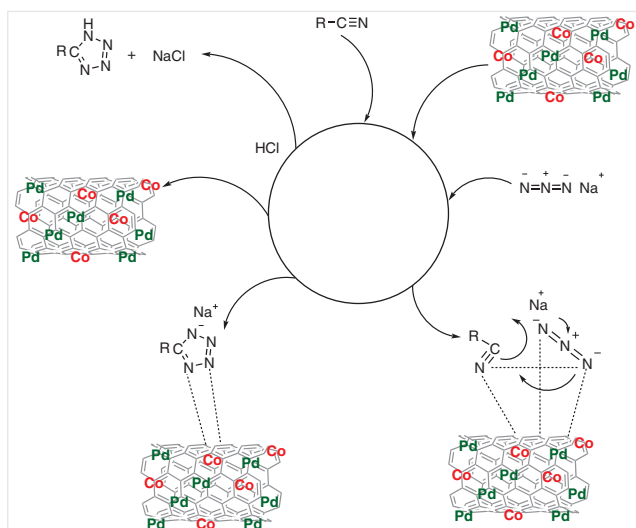
Scheme 5 Mechanism for the synthesis of 5-substituted 1*H*-tetrazoles catalyzed by Mw-Pd/Co@CNT NPs. Reprinted with permission from ref. 47. Copyright 2016 Wiley-VCH.
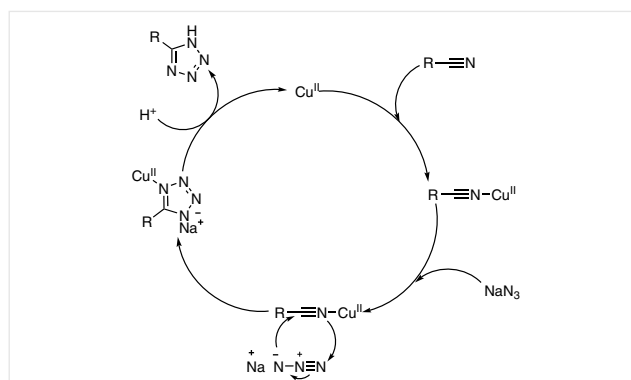
Scheme 6 Mechanism for the synthesis of 5-substituted 1*H*-tetrazoles via [3+2]-cycloaddition reaction between nitrile derivatives and sodium azide in the presence of a heterogeneous Cu(II)

yields (45–93%) in 3–30 minutes under controlled microwave heating at 230 °C. The advantages of this procedure were short reaction time, recyclability of the catalyst, and simple workup procedure.
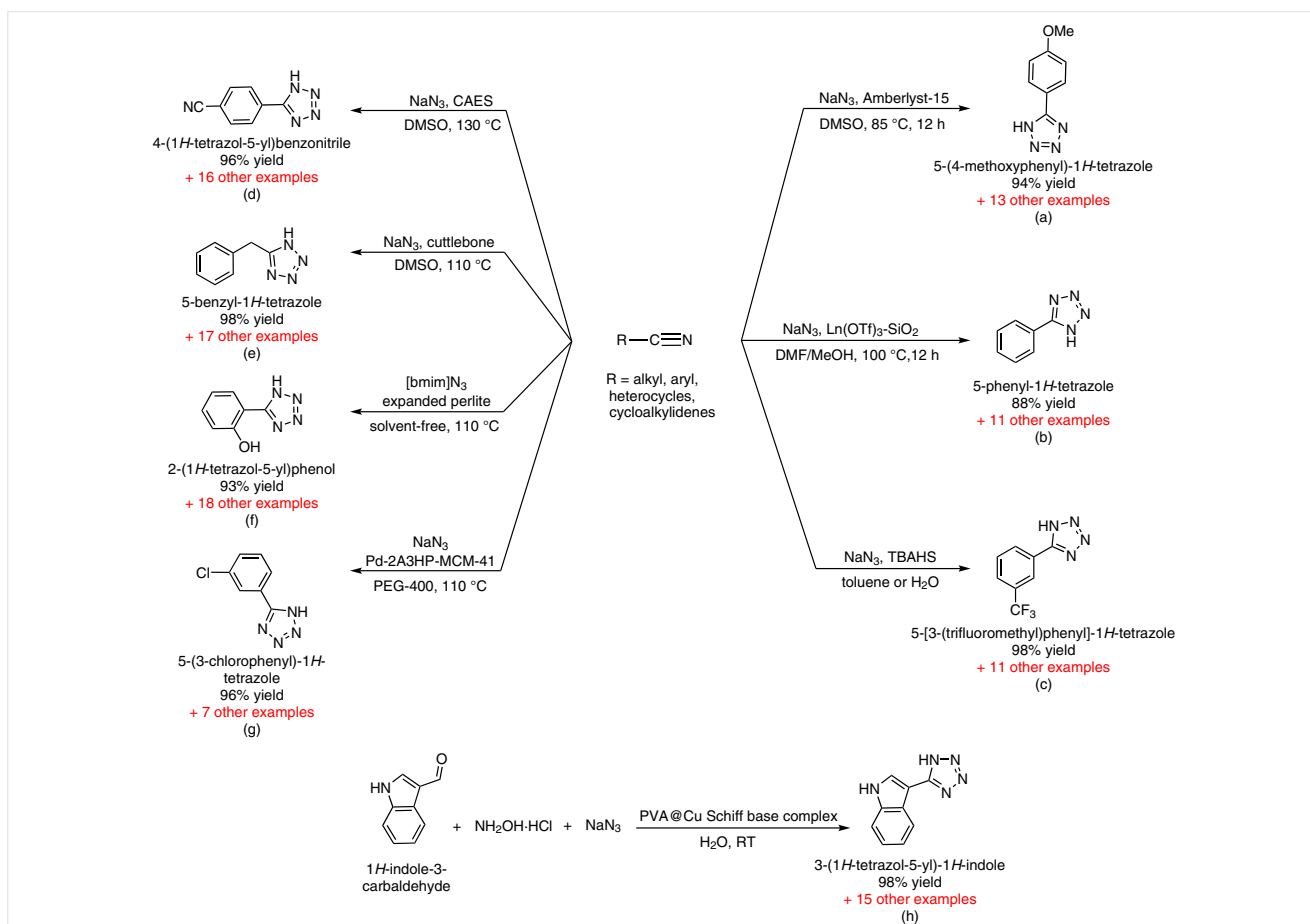
Scheme 7 Examples of the synthesis of 5-substituted 1*H*-tetrazoles using heterogeneous catalysts

3.2   Heterogeneous Catalysts

Heterogeneous catalysis is a form of catalysis where the phase of the catalyst differs from that of the reactants. Early homogeneous catalysts used for the synthesis of 5-substituted 1*H*-tetrazoles had drawbacks like tedious separation procedures, poor recovery, and recyclability. To overcome these challenges, heterogeneous catalysts were developed and they have become a popular choice for the synthesis of 5-substituted 1*H*-tetrazoles.

An efficient procedure for the synthesis of 5-substituted 1*H*-tetrazoles using solid acid resin Amberlyst-15 as a heterogeneous catalyst was reported by Nagarkar and co-workers (Scheme 7a).[49] The optimum conditions used DMSO as a solvent at 85 °C for 12 hours giving the products in high yields (36–94%); the highest yield was obtained for 4-methoxybenzonitrile, which gave 5-(4-methoxyphenyl)-1*H*-tetrazole in 94% yield. The catalyst was recovered by simple filtration and reused.

Silica-supported lanthanum triflate $(Ln(OTf)_3\text{-}SiO_2)$ was used by Meshram and co-workers[50] for the synthesis of 5-substituted 1*H*-tetrazoles via [3+2] cycloaddition of aromatic/heteroaromatic nitriles and sodium azide (Scheme 7b). Conventionally DMSO or DMF is used as a solvent for these cycloaddition reactions, but in this case DMF/MeOH (4:1) was optimal to give the products in up to 88% yield in a short reaction time. A few noticeable features of this heterogeneous catalyst were nontoxicity, good recovery, and recyclability.

5-Substituted 1*H*-tetrazoles were synthesized by Cheon and co-workers by the treatment of nitriles with sodium azide in the presence of water or toluene using tetra-butylammonium hydrogen sulfate (TBAHS) as solid acid catalyst (Scheme 7c).[51] To make procedure environmentally benign, water was used as a solvent and the results were compared to experiments using toluene. Using water reduced the time required, but the products were obtained in lower yields compared to toluene. The reaction in water gave products in 53–98% yield with 3-(trifluoromethyl)benzonitrile giving 5-[3-(trifluoromethyl)phenyl]-1*H*-tetrazole in the maximum yield of 98%.

Cu(II) immobilized on aminated epichlorohydrin activated silica (CAES) in DMSO was used as a catalyst by the Akhlaghinia group for the synthesis of 5-substituted 1*H*-tetrazoles (Scheme 7d).[52] The mechanism proposes initial activation of the nitrogen atom of the nitrile by Cu(II), which accelerates the [3+2] cycloaddition. This is followed by acidic workup to give 5-substituted 1*H*-tetrazoles. The catalyst was recovered and reused up to five times. Yields were generally high (75–96%) with the highest yield (96%) for the reaction of terephthalonitrile (benzene-1,4-dicarbonitrile) to give 5-(4-cyanophenyl)-1*H*-tetrazole.

The Akhlaghinia group[53] used cuttlebone to catalyze the [3+2]-cycloaddition reaction nitriles and sodium azide in DMSO at 110 °C to give 5-substituted 1*H*-tetrazoles (Scheme 7e). Cuttlebone is a biomaterial that possesses high porosity, compressive strength, flexural stiffness, and thermal stability. The electrophilic activation of the nitrile through hydrogen bond formation between the cuttlebone and the nitrile drives the [3+2]-cycloaddition reaction. The catalyst was easily recovered and was reused seven times. Excellent yields (85–98%) of products were obtained with the highest yield (98%) observed for the reaction of benzonitrile, terephthalonitrile, 4-nitrobenzonitrile, and also 2-phenylacetonitrile.

The Akhlaghinia group[54] synthesized 5-substituted 1*H*-tetrazoles via the [3+2] cycloaddition of nitriles with [bmim]N$_3$ ionic liquid (azide source) using expanded perlite as a heterogeneous catalyst under solvent-free conditions (Scheme 7f). Expanded perlite is naturally glassy volcanic rock usually containing 2–6% water. The procedure is environmentally benign and produced the 5-substituted 1*H*-tetrazoles in excellent yields (84–96%). The maximum yield was produced when terephthalonitrile was used. The catalyst was recovered and reused six times.

Nikoorazm and co-workers[55] synthesized a heterogeneous catalyst by anchoring palladium onto the surface of organically modified mesoporous silica (Pd-2A3HP-MCM-41) and then used this catalyst in PEG-400 for the synthesis of 5-substituted 1*H*-tetrazoles (Scheme 7g). Aromatic nitriles with electron-withdrawing substituents gave excellent yields in lower reaction times in comparison to electron-donating substituents. The catalyst was easily separated from the reaction mixture by filtration. The recovered catalyst was used more than seven times with a slight change in its activity. The highest yield of 96% was observed in cases of terephthalonitrile and 3-chlorobenzonitrile.

Polyvinyl alcohol immobilized copper(II) Schiff base complex [PVA@Cu(II) Schiff base complex] in water was used by Sardarian and Kazemnejadi[56] for an environmentally benign one-pot three-component synthesis of 5-substituted 1*H*-tetrazoles via click reaction of aliphatic and aromatic aldehydes with hydroxylamine hydrochloride and sodium azide at room temperature (Scheme 7h). Mechanistically, the oxime is formed first, this is followed by [3+2]-cycloaddition reaction between the oxime and hydrazoic acid, and finally elimination of a molecule of water gives the tetrazoles (Scheme 8). The structure of the catalyst contains both lipophilic (C–C and C–H bonds) and hydrophilic parts (polar groups and copper complex), and for this reason the substrates are easily dissolved and remain in close proximity due to hydrogen bonding and coordination with copper(II). Most aldehydes gave the product 5-substituted 1*H*-tetrazoles in excellent yields of up to 98%.

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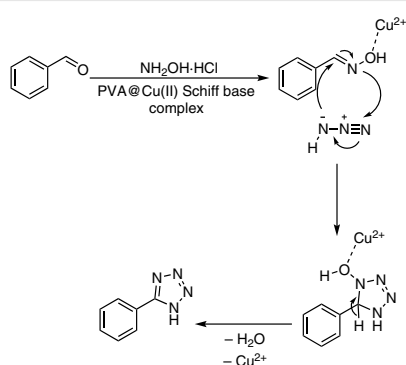
Scheme 8 Mechanism for the formation of 5-substituted 1*H*-tetrazoles using PVA@Cu(II) Schiff base complex

3.3 Nanoparticles as Heterogeneous Catalysts

Nanocatalysts/nanoparticles play an important role in green synthesis. By decreasing the size of the catalyst, advantages such as availability of larger surface area to the reactant and the requirement of only a negligible amount of catalyst to give significant results are obtained. Moreover, better selectivity can be achieved, thus, eliminating the formation of undesired products.[57]

5-(Alkylthio)- and 5-(arylthio)-1*H*-tetrazoles were synthesized in up to 94% yields by Kolo and Sajadi[58] from thiocyanates using Fe_3O_4 NPs, which are magnetically recoverable and reusable (Scheme 9). Mechanistically, the catalyst activated the nitrile group on its surface by forming a complex with the nitrile group of the thiocyanate, thus imparting electrophilic character. Subsequently, nucleophilic attack of sodium azide takes place. The catalyst was easily recovered and reused with no significant loss in its catalytic activity.
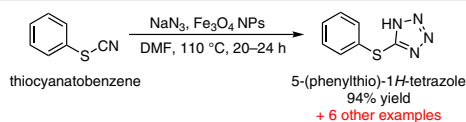
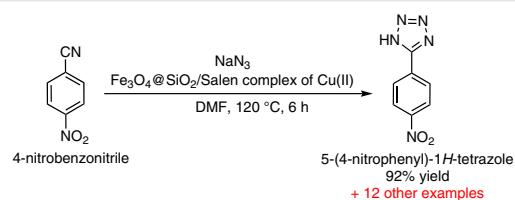**Scheme 9** Fe_3O_4 NPs catalyzed synthesis

5-Substituted 1*H*-tetrazoles were synthesized in good to excellent yields (75–98%) using 4′-phenyl-2,2′:6′,2″-terpyridine–copper(II) complex immobilized onto activated multi-walled carbon nanotubes [AMWCNTs-O-Cu(II)-PhTPY] in DMF at 70 °C by Sharghi and co-workers (Scheme 10).[59] The catalyst displayed good reusability for up to five cycles.

The Salen complex of Cu(II) supported on superparamagnetic $Fe_3O_4@SiO_2$ nanoparticles [$Fe_3O_4@SiO_2$/Salen complex of Cu(II)] was reported as a catalyst by Sardarian and co-workers for the formation 5-substituted 1*H*-tetrazoles in DMF at 120 °C (Scheme 11).[41e] The catalyst was easily recovered using an external magnet and was reused up
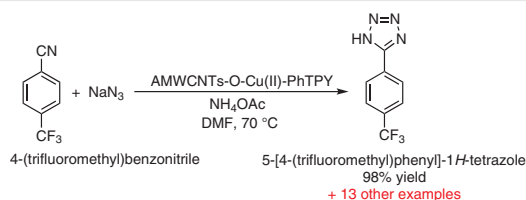

Scheme 10 AMWCNTs-O-Cu(II)-PhTPY-catalyzed synthesis

to seven times with no significant loss in its activity. The maximum yield of up to 92% was attained when using 4-nitrobenzonitrile or terephthalonitrile.


Scheme 11 $Fe_3O_4@SiO_2$/Salen complex of Cu(II) catalyzed synthesis

Silver NPs (Ag NPs) in DMF at 120 °C were utilized by Awasthi and co-workers[41f] for the synthesis of 5-substituted 1*H*-tetrazoles in up to 93% yield (Scheme 12). Mechanistically, the nitrogen atom of the nitrile group is activated by Ag NPs, thus imparting electrophilic character to the carbon atom of nitrile group. Further, nucleophilic attack by sodium azide leads to the formation of tetrazoles.
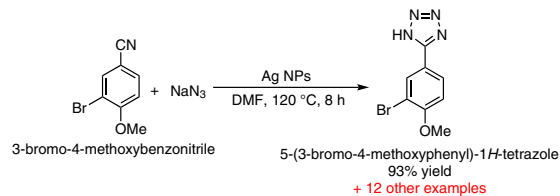
**Scheme 12** Ag NPs catalyzed synthesis

Javidi and co-workers[60] synthesized 5-substituted 1*H*-tetrazoles in good to excellent yields (83–97%) using a recyclable ligand complex of copper(II) supported on superparamagnetic $Fe_3O_4@SiO_2$ nanoparticles in DMF at 110 °C (Scheme 13). The catalyst was easily recovered using an ex-
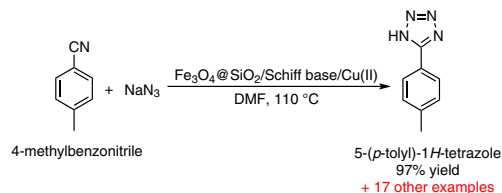

Scheme 13 Cu(II) supported on superparamagnetic $Fe_3O_4@SiO_2$ NPs catalyzed synthesis

ternal magnet and was reused up to six times with negligible deterioration in its catalytic activity. The maximum yield was achieved using 4-methylbenzonitrile and 4-methoxybenzonitrile as substrates.

(*E*)-Aldoximes and sodium azide underwent a copper ferrite nanoparticles (CuFe₂O₄ NPs) mediated reaction in DMF at 120 °C for 12 hours to give 5-substituted 1*H*-tetrazoles in up to 92% yields as reported by Banda and co-workers (Scheme 14).[61] Mechanistically, the reaction does not follow a nitrile formation pathway, instead the nucleophilic azide attacks the electron-deficient carbon of the oxime which promotes the reaction through cycloaddition. The catalyst plays a role in activating the oxime by coordination with the oxygen of oxime which further promotes C=N towards the cycloaddition reaction with NaN₃.


Scheme 14   CuFe₂O₄-catalyzed synthesis
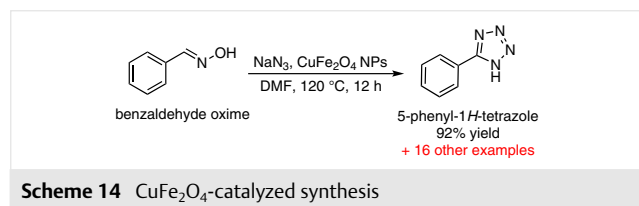
In 2015, Abdollahi-Alibeik and Moaddeli[62] reported a multicomponent, one-pot reaction of an aldehyde, hydroxylamine, and sodium azide for the synthesis of 5-substituted 1*H*-tetrazoles using Cu-MCM-41 NPs as a catalyst (Scheme 15, top). Cu-MCM-41 NPs with three Cu/Si molar ratios (viz. 0.1, 0.05, and 0.033) were prepared. Amongst these, the catalyst with Cu/Si molar ratio of 0.05 displayed highest catalytic activity. The catalyst could be recovered and reused up to three times with moderate loss in its catalytic activity. 3-Bromobenzaldehyde produced the highest yield (94%). In 2016, they also reported the synthesis of 5-substituted 1*H*-tetrazoles by [3+2]-cycloaddition reaction between nitriles and sodium azide using the same Cu-MCM-41 NPs as the catalyst (Scheme 15, bottom).[63]

Scheme 15   Cu-MCM-41-catalyzed synthesis
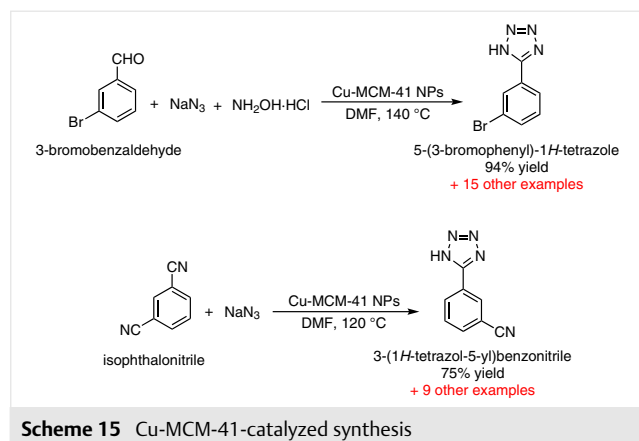
The gold nanoparticles [Au NPs, Au(0)] and gold(III) chloride [HAuCl₄·3H₂O, Au(III)] catalyzed synthesis of 5-substituted 1*H*-tetrazoles in DMF was reported by Awasthi, Agarwal, and co-workers (Scheme 16).[41g] Mechanistically, the C≡N functionality is activated through coordination to Au(III), followed by nucleophilic addition of NaN₃, and finally protonolysis to form 5-substituted 1*H*-tetrazoles via a [3+2]-cycloaddition reaction. A similar mechanism is anticipated for Au(0) NPs. Au(0) displayed better reactivity giving higher yields in less time. This may be due to the larger surface area of Au(0) NPs that facilitates better coordination between C≡N and Au(0). The use of Au(0) NPs gave 5-substituted 1*H*-tetrazoles in 83–99% yields (16 examples), while the use of Au(III) gave the same products in 82–98% yields.
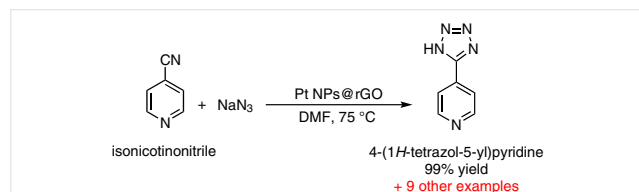

Scheme 16   Au NPs catalyzed synthesis
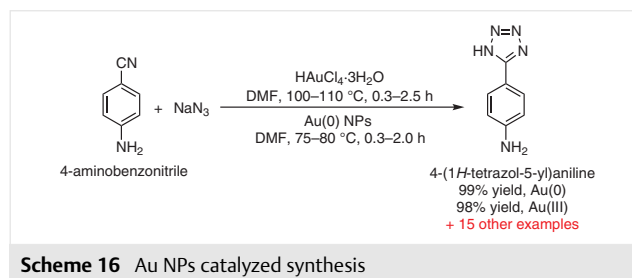
5-Substituted 1*H*-tetrazoles were synthesized by treatment of a nitrile and sodium azide with nano-TiCl₄·SiO₂ as a solid Lewis acid catalyst in DMF under reflux for 2 hours by Zamani and co-workers (Scheme 17).[64] The catalyst was recoverable and was reused up to three times without significant loss in its catalytic activity. This protocol was applied to aryl, heteroaryl, and benzyl cyanides and gave the corresponding 5-substituted 1*H*-tetrazoles in good to excellent yields (78–95%). The 5-substituted 1*H*-tetrazoles synthesized had no antifungal activity against the fungi examined and they did not inhibit the growth of Gram-positive and Gram-negative bacteria at concentrations up to 256 μg mL⁻¹.

**Scheme 17**   Nano-TiCl₄·SiO₂-catalyzed synthesis
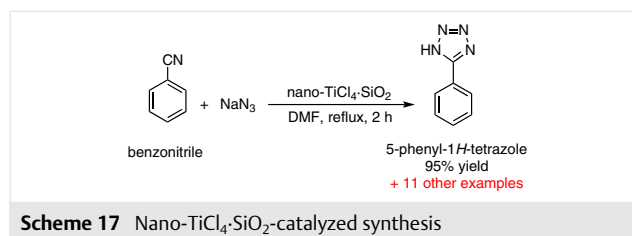
A range of benzonitriles and sodium azide underwent [3+2] cycloaddition using monodisperse platinum nanoparticles supported with reduced graphene oxide (Pt NPs@rGO) as a heterogeneous catalyst as reported by Kaya, Sen, and co-workers (Scheme 18).[41j] 5-Aryl- and 5-heteroaryl-1*H*-tetrazoles were obtained in high yields (87–99%) in

a short reaction time (0.4–5 hours). The catalyst could be recovered and reused for up to six times with no significant loss in its catalytic activity.


Scheme 18 Pt NPs@rGO catalyzed synthesis

Kaya, Sen, and co-workers[65] also synthesized 5-aryl- and 5-heteroaryl-1*H*-tetrazoles in excellent yields (89–99%) using monodisperse platinum nanoparticles decorated on activated carbon (Pt NPs@AC) in DMF using microwave irradiation in a short reaction time (90 °C, 140 W, fixed mode, 10–30 min) (Scheme 19). The proposed reasons for the high catalytic activity of Pt NPs@AC are low crystalline particle size, high chemical surface area, and high %Pt(0) content.
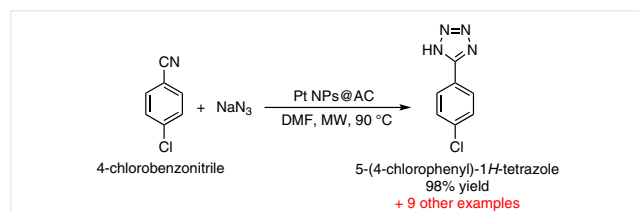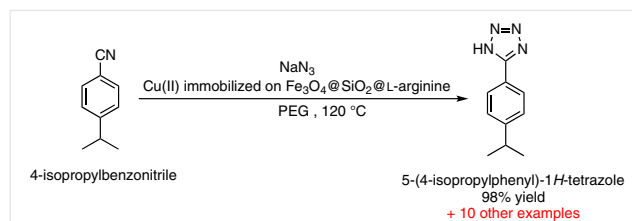

Scheme 19 Pt NPs@AC catalyzed synthesis

A magnetically separable and ecofriendly nanocatalyst magnetite-chitin (Fe$_3$O$_4$@chitin) was synthesized by the Akhlaghinia group and used in a green synthesis of 5-substituted 1*H*-tetrazoles.[66] Starting from a range of alkanenitriles, benzonitriles, and heteroarenecarbonitriles using 1-butyl-3-methylimidazolium ([bmim]N$_3$) under solvent-free conditions for a short reaction time (15–120 min) gave the product 5-alkyl-, 5-aryl-, and 5-heteroaryl-1*H*-tetrazoles in excellent reaction yields (70–98%), with the highest yield observed starting from 4-nitrobenzonitrile (Scheme 20). The catalyst was recovered using an external magnet and reused for six cycles with no significant loss in its catalytic activity.
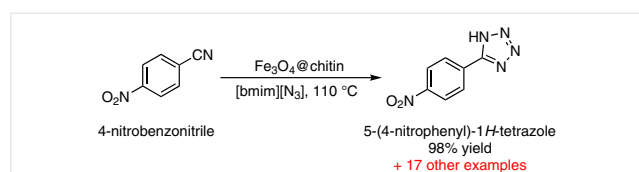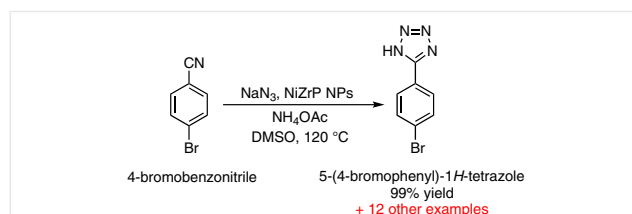

Scheme 20 Fe$_3$O$_4$@chitin-catalyzed synthesis

Cu(II) immobilized on Fe$_3$O$_4$@SiO$_2$@L-arginine is an inexpensive and non-corrosive catalyst that was used by

Scheme 21 Cu(II) immobilized on Fe$_3$O$_4$@SiO$_2$@L-arginine catalyzed synthesis

Ghorbani-Choghamarani and co-workers[67] for the synthesis of 5-aryl-1*H*-tetrazoles in good to excellent yields (60–98%) via cycloaddition reaction of various benzonitriles with sodium azide in polyethylene glycol (PEG) (Scheme 21). The catalyst displayed high efficiency and recoverability by an external magnet and it was reused up to four times in this protocol.

The [3+2]-cycloaddition reaction of sodium azide with various nitriles (alkanenitriles, benzonitriles, heteroarenecarbonitriles) using nickel zirconium phosphate (NiZrP) nanocatalyst in DMSO at 120 °C was utilized by Abrishami and co-workers for the synthesis of 5-substituted 1*H*-tetrazoles (Scheme 22).[68] The catalyst could be reused up to five cycles without significant loss in its catalytic activity. The 5-substituted 1*H*-tetrazoles were obtained in excellent yields (60–99%), with 4-bromobenzonitrile producing the maximum yield.
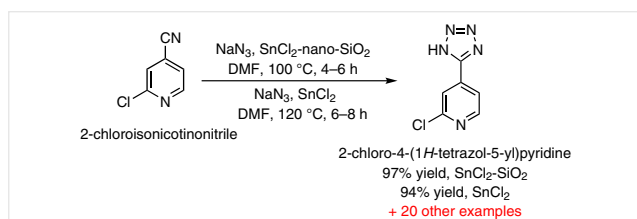

Scheme 22 NiZrP NPs catalyzed synthesis

In 2016, Esmaeilpour, Zahmatkesh, and Javidi[69] reported the one-pot synthesis of 5-substituted 1*H*-tetrazoles in excellent yields (83–96%) using 1,4-dihydroxyanthraquinone–copper(II) supported on Fe$_3$O$_4$@SiO$_2$ [Fe$_3$O$_4$@SiO$_2$-DAQ-Cu(II)] as a magnetically recoverable catalyst (Scheme 23). The catalyst could be reused up to six cycles without significant loss in its catalytic activity.
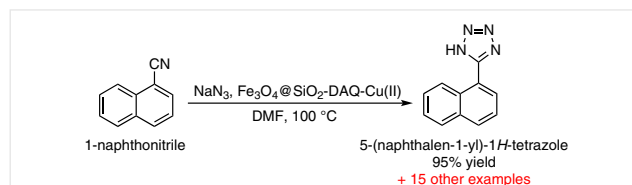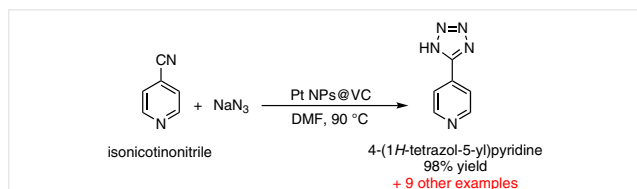

Scheme 23 Fe$_3$O$_4$@SiO$_2$-DAQ-Cu(II)-catalyzed synthesis

A comparative study between heterogeneous tin(II) chloride loaded silica nanoparticles (SnCl₂-nano-SiO₂) and homogeneous tin(II) chloride for the synthesis of 5-substituted 1*H*-tetrazoles in DMF was reported by Awasthi and co-workers (Scheme 24).[41k] SnCl₂-nano-SiO₂ was found to be more efficient compared to SnCl₂ due to its higher surface area, larger pore volume, and recyclability. A range of 5-aryl-, 5-heteroaryl-, and 5-benzyl-1*H*-tetrazoles were synthesized in 82–98% yields using SnCl₂-nano-SiO₂ and 78–94% using SnCl₂.


Scheme 24 SnCl₂-nano-SiO₂-catalyzed synthesis

5-Substituted 1*H*-tetrazoles were synthesized in excellent yields (87–98%) by Kaya, Sen, and co-workers in a reaction catalyzed by monodisperse carbon black decorated platinum nanoparticles (Pt NPs@VC) in DMF at 90 °C for a short reaction time (0.5–5 hours) (Scheme 25).[70] The reusability performance of Pt NPs@VC was compared with that of previously reported heterogeneous catalysts. Pt NPs@VC displayed a very high TOF value of 44.86 h⁻¹ compared to other catalysts, the only exception being Pt NPs@rGO.[41j]
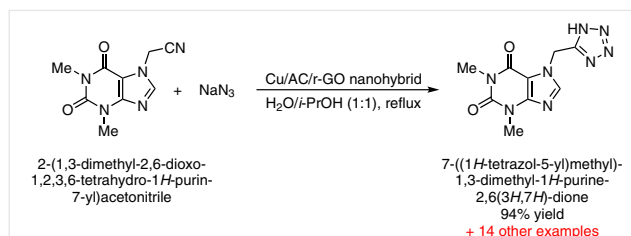

Scheme 25 Pt NPs@VC catalyzed synthesis

Further to their work with Fe₃O₄@SiO₂@ʟ-arginine (Scheme 21),[67] Ghorbani-Choghamarani and co-workers[71] used Cu(II)-immobilized on Fe₃O₄@SiO₂@ʟ-histidine as a catalyst for the synthesis of 5-substituted 1*H*-tetrazoles in high yields (70–98%) via cycloaddition reaction of various nitriles with sodium azide in PEG (Scheme 26). The catalyst displayed high efficiency, it could be recovered by an external magnet, and it could be reused up to five times in the protocol.

5-Substituted 1*H*-tetrazoles bearing bioactive *N*-heterocyclic cores were synthesized in good to excellent yields (75–94%) by Soltani Rad, Behrouz, and co-workers via [3+2]-cycloaddition reaction between heteroarylacetonitriles and sodium azide in the presence of Cu/aminoclay/re-
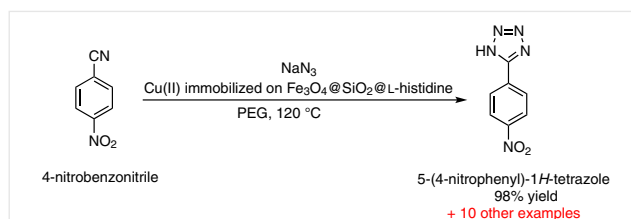

Scheme 26 Cu(II) immobilized on Fe₃O₄@SiO₂@ʟ-histidine catalyzed synthesis

duced graphene oxide nanohybrid (Cu/AC/r-GO nanohybrid) as a heterogeneous nanocatalyst in water/*i*-PrOH (50:50) media under reflux conditions (Scheme 27).[72] The catalyst and solvent system used in the synthesis are environmentally benign. The catalyst displayed good recyclability and reusability.


Scheme 27 Cu/AC/r-GO nanohybrid catalyzed synthesis

The [3+2] cycloaddition of benzonitriles with sodium azide in the presence of the *S*-methylisothiourea complex of palladium immobilized on boehmite nanoparticles (Pd-SMTU@boehmite) in PEG-400 at 120 °C to give 5-aryl-1*H*-tetrazoles in excellent yields (up to 95%) was reported by Ghorbani-Choghamarani and Moradi (Scheme 28).[73] The catalyst could be reused for up to ten cycles without significant loss in its activity and it displayed TOF value of 12.66 h⁻¹.
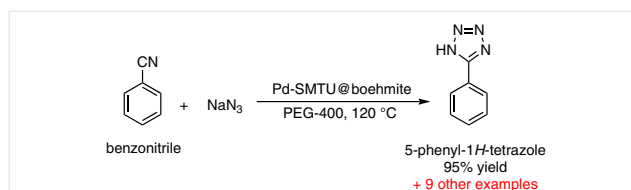
Scheme 28 Pd-SMTU@boehmite-catalyzed synthesis

A magnetically recoverable Ni(II) complex supported on Fe₃O₄@SiO₂ nanoparticles [Fe₃O₄@SiO₂@DOPisatin-Ni(II), DOP= dopamine] was used for the synthesis of 5-aryl-1*H*-tetrazoles in 71–92% yields in PEG at 120 °C by Hajjami and co-workers (Scheme 29).[74] Mechanistically, it is proposed that the catalyst first coordinates with the azide followed by [3+2]-cycloaddition reaction between a benzonitrile and catalyst coordinated azide to afford the 5-aryl-1*H*-tetrazole.
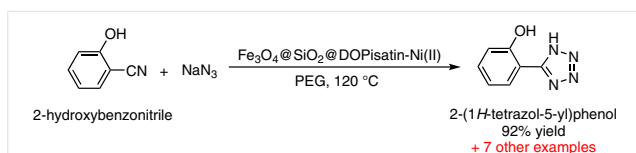
Scheme 29 Fe$_3$O$_4$@SiO$_2$@DOPisatin-Ni(II)-catalyzed synthesis

In 2018, Sardarian and co-workers[75] used a magnetically recoverable Cu(II) complex supported on Fe$_3$O$_4$@SiO$_2$ coated by polyvinyl alcohol (PVA) [Fe$_3$O$_4$@SiO$_2$-TCT-PVA-Cu(II), TCT = 2,4,6-trichlorotriazine or cyanuric chloride] for the synthesis of 5-aryl-1H-tetrazoles and 5-phenethyl-1H-tetrazole from aldehydes, hydroxylamine hydrochloride, and sodium azide in water under reflux conditions (Scheme 30). The highest yield of 96% was observed when benzaldehyde and 4-nitrobenzaldehyde were used.
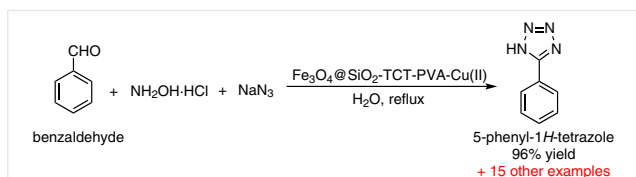
Scheme 30 Fe$_3$O$_4$@SiO$_2$-TCT-PVA-Cu(II)-catalyzed synthesis

Cu(II)-Adenine-MCM-41 was used to catalyze the [3+2] cycloaddition of nitriles and sodium azide in PEG-400 at 130 °C by Nikoorazm and co-workers[76] to give 5-substituted 1H-tetrazoles in up to 95% yields (Scheme 31). The catalyst could be reused in up to six cycles without any significant loss in its catalytic activity.
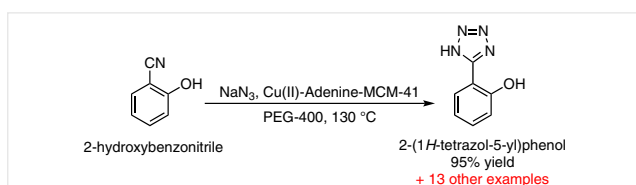

Scheme 31 Cu(II)-Adenine-MCM-41-catalyzed synthesis

3.4 Miscellaneous Methods

A single-step synthesis of 5-substituted 1H-tetrazoles by Sridhar and co-workers[77] used the reaction of aldehydes with acetohydroxamic acid and sodium azide catalyzed by bismuth(III) triflate in DMF at 120 °C (Scheme 32). 5-Aryl-, 5-heteroaryl-, 5-alkyl-, and 5-vinyl-1H-tetrazoles were synthesized in 15–28 hours and moderate to good yields (60–87%) were obtained. The highest yield was observed when benzaldehyde was used.
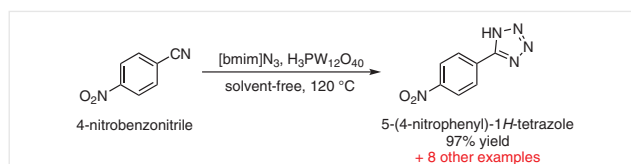

Scheme 33 H$_3$PW$_{12}$O$_{40}$-catalyzed synthesis
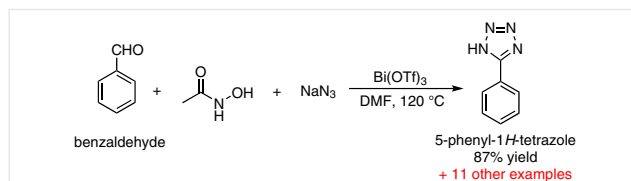
Scheme 32 Bi(OTf)$_3$-catalyzed synthesis

A green synthesis of 5-alkyl- and 5-aryl-1H-tetrazoles in high yields (89–97%) catalyzed by heteropolyacid (H$_3$PW$_{12}$O$_{40}$) using nitriles and [bmim]N$_3$ under solvent-free conditions at 120 °C for 5–12 hours was reported by Heravi and co-workers (Scheme 33).[78] 4-Nitrobenzonitrile produced the highest yield.

The synthesis of 5-substituted 1H-tetrazoles promoted by β-cyclodextrin (β-CD) via [3+2]-cycloaddition reaction between nitriles and sodium azide in the presence of ammonium chloride using DMF as solvent at 120 °C was reported by Dalal and co-workers (Scheme 34).[79] Cyclodextrins are cyclic oligomers of D-glucose that are named as α-, β-, and γ-cyclodextrin for the hexamer, heptamer, and octamer, respectively.[80] They are known to catalyze reactions through supramolecular catalysis that involves the formation of host–guest complexes by non-covalent bonding interactions.[81] Cyclodextrins have an internal cavity that is hydrophobic in nature, which enables it to bind with a variety of guest molecules.[82] β-Cyclodextrin is a nontoxic catalyst displayed good efficiency and gave 5-alkyl-, 5-benzyl-, and 5-aryl-1H-tetrazoles in high yields (70–95%) in a short reaction time. The catalyst could be recovered and reused several times without significant loss in its catalytic activity.
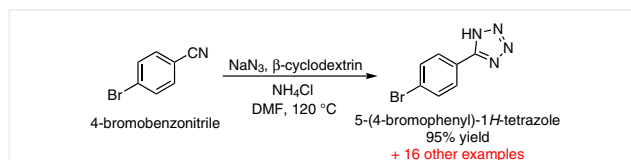
Scheme 34 β-Cyclodextrin-catalyzed synthesis

An efficient method to recycle tributyltin chloride from tributyltin hydroxide was developed by Sampath and co-workers. The recycled tributyltin chloride was then used as a reagent in the reaction of nitriles with sodium azide to

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give 5-alkyl-, 5-benzyl-, and 5-aryl-1*H*-tetrazoles in 73–89% yields (Scheme 35).[83] This route offers the possibility to significantly save on toxic tin waste.
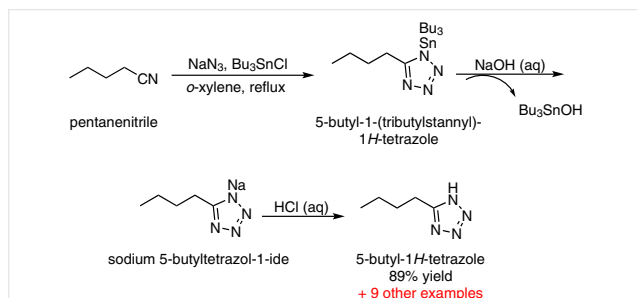
Scheme 35 Synthesis using tributyltin chloride recycled from tributyltin hydroxide

Lin and co-workers[84] for the first time reported a click-type cycloaddition reaction between various boron azides and nitriles to give 5-substituted 1*H*-tetrazoles using ammonium acetate as the catalyst in DMF/MeOH (9:1) solvent system at 100 °C (Scheme 36). After optimization, LiB(N$_3$)$_4$ along with 10 mol% ammonium acetate was found to be the best reaction condition. A plausible mechanism has been proposed for the synthesis (Scheme 37). The method was quite economical and proceeded under mild conditions. The maximum yield (96%) was achieved in case of 4-nitrophthalonitrile.
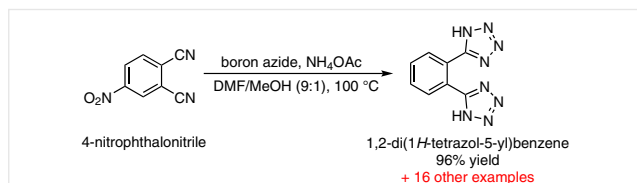
Scheme 36 Synthesis using boron azides (LiB(N$_3$)$_4$) and nitriles
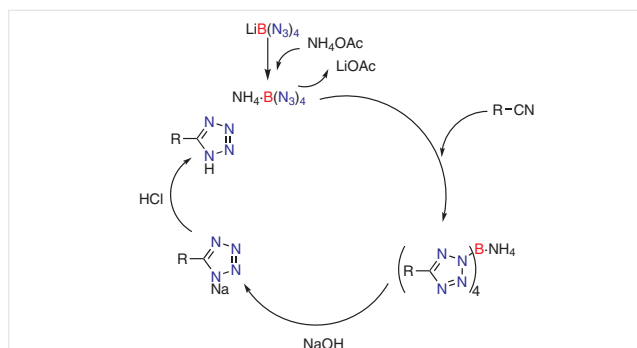
Scheme 37 Proposed mechanism for the synthesis using lithium tetraazidoborate and nitriles

A new protocol for the synthesis of 5-alkyl-, 5-benzyl-, and 5-aryl-1*H*-tetrazoles in moderate to excellent yields (51–95%) by the treatment of nitriles with sodium azide us-

ing zinc(II) chloride as a catalyst and aliphatic alcohols as solvent for a short reaction time was reported by Myznikov and co-workers (Scheme 38).[85] The protocol was also applicable to deactivated aliphatic nitriles.

Scheme 38 ZnCl$_2$-catalyzed synthesis in aliphatic alcohols

An environmentally benign, one-pot synthesis of 5-substituted 1*H*-tetrazoles in good yields ('nearly 80%') from aldehydes or ketones, malononitrile, and sodium azide via Knoevenagel condensation and 1,3-dipolar cycloaddition reactions under mild conditions without any catalyst in water was reported by Mahkam and co-workers (Scheme 39).[86]
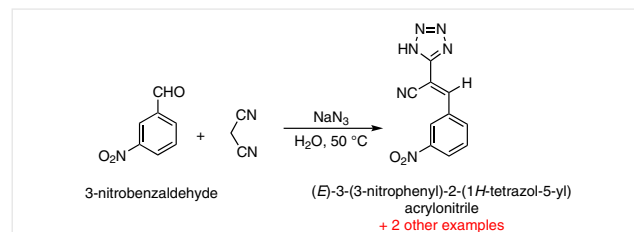
Scheme 39 Catalyst-free synthesis in water as solvent

5-Substituted 1*H*-tetrazoles were synthesized in up to 98% yields by Coca and Turek[87] by reaction between aryl-, alkyl-, and vinyl-substituted nitriles with sodium azide using ytterbium triflate hydrate in DMF at 120–140 °C (Scheme 40). Substrates containing electron-withdrawing groups were more reactive than those containing electron-donating groups. Aryl-substituted nitriles were more reactive than alkyl-substituted nitriles.
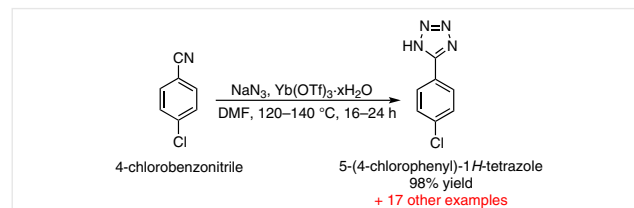
Scheme 40 Yb(OTf)$_3$·xH$_2$O-catalyzed synthesis

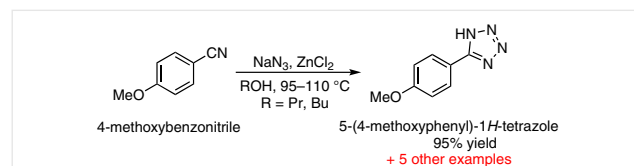The one-pot synthesis of 5-substituted 1*H*-tetrazoles via [3+2]-cycloaddition reaction between nitriles and sodium azide using silver nitrate as a catalyst in refluxing DMF was reported by Awasthi and co-workers (Scheme 41).[88] Mechanistically, the reaction occurs via in situ formation of silver

azide, which coordinates with the nitrile, and this is followed by [3+2]-cycloaddition reaction to afford 5-substituted 1*H*-tetrazoles in good yields (76–87%) in 5 hours. 4-Acetamido-3-nitrobenzonitrile produced the corresponding 1*H*-tetrazole with the highest yield.
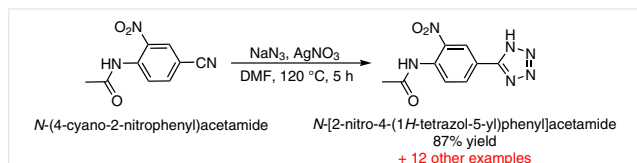
Scheme 41   AgNO$_3$-catalyzed synthesis

The [3+2]-cycloaddition reaction of nitriles with sodium azide using immobilized AlCl$_3$ on γ-Al$_2$O$_3$ as a reusable catalyst in DMF at 50 °C for a short reaction time (1–3 hours) gave 5-substituted 1*H*-tetrazoles in excellent yields (83–96%) as reported by Nanjundaswamy and Abrahamse (Scheme 42).[89] This procedure was environment friendly and the catalyst could be recycled.

Scheme 42   Reaction catalyzed by AlCl$_3$ on γ-Al$_2$O$_3$

In 2014, Awasthi and co-workers[39b] reported an efficient procedure for the synthesis of 5-benzyl- or 5-aryl-1*H*-tetrazoles in excellent yields (82–99%) via [3+2]-cycloaddition reaction between nitriles and sodium azide using ceric ammonium nitrate as a catalyst in DMF at 110 °C for 6 hours (Scheme 43).

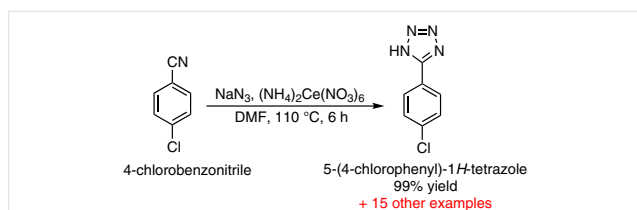**Scheme 43**   Ceric ammonium nitrate catalyzed synthesis

4-(Dimethylamino)pyridinium acetate is a recyclable catalyst with ionic liquid character that was used by Nowrouzi and co-workers[90] for the [3+2]-cycloaddition reaction between nitriles and sodium azide under solvent-free conditions at 100 °C to give 5-substituted 1*H*-tetrazoles

(Scheme 44). The workup procedure did not require acidification (use of HCl) and the 5-substituted 1*H*-tetrazoles were obtained in up to 98% yields.
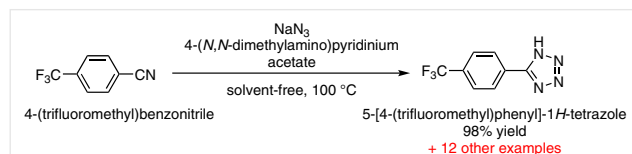
Scheme 44   4-(Dimethylamino)pyridinium acetate catalyzed synthesis under solvent-free conditions

Cyanuric chloride is easily available and inexpensive. It was used as a catalyst for the synthesis of 5-substituted 1*H*-tetrazoles in high yields (up to 93%) in DMF at 120 °C for a short reaction time (2–5 hours) by Lalitha and co-workers (Scheme 45).[91]
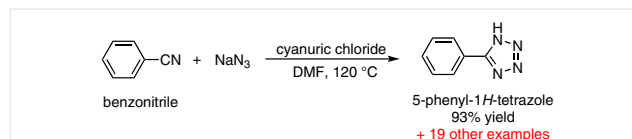
Scheme 45   Cyanuric chloride catalyzed synthesis

The non-metal catalyst graphene was utilized by Qi and co-workers[41h] for the synthesis of 5-substituted 1*H*-tetrazoles in DMF at 120 °C for 36 hours (Scheme 46); the catalyst was separated from reaction mixture by simple centrifugation. The protocol afford tetrazoles in moderate yields (60–73%) only.
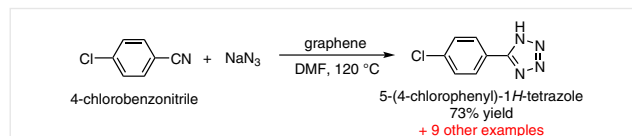
Scheme 46   Graphene-catalyzed synthesis

The copper nitrate catalyzed reaction of alcohols or aldehydes and sodium nitrite to give 5-substituted 1*H*-tetrazoles was reported by Tao and co-workers (Scheme 47).[92] The proposed mechanism proceeds through the Cu(NO$_3$)$_2$-catalyzed oxidation of the alcohol to an aldehyde, followed by condensation with ammonia to form a primary imine intermediate. Oxidation of the imine affords a nitrile; coordination of Cu(NO$_3$)$_2$ to electrophilic nitrile group assists nucleophilic attack by azide, which is followed by cycloaddition to give the product 5-substituted 1*H*-tetrazoles. The use of alcohol substrate gave tetrazoles in up to 86% yields whereas aldehydes gave up to 82% yields.

The reaction of oximes and sodium azide catalyzed by indium(III) chloride in DMF at 120 °C for 10–48 hours to give various 5-substituted 1*H*-tetrazoles in up to 95% was reported by Babu and co-workers (Scheme 48).[93] In com-

Review

Scheme 47 Cu(NO$_3$)$_2$-catalyzed synthesis using aldehydes and alcohols
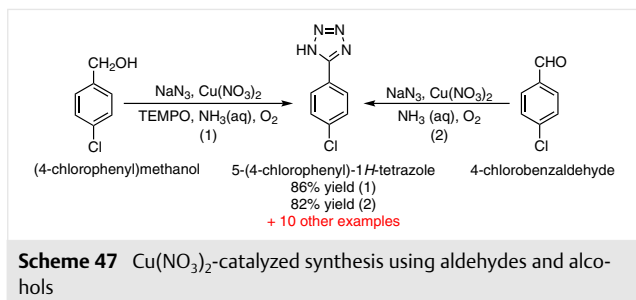
parison to nitrile-based approaches, it was found that aryl oximes bearing electron-donating groups gave the best yields (82–95%) in the shortest reaction times (10–14 hours), and aryl oximes bearing electron-withdrawing groups reacted more slowly (18–21 hours) and gave lower yields (82–90%). 5-Heteroaryl-1H-tetrazoles were generally obtained in good yields, but 5-alkyl-1H-tetrazoles were obtained in poor yields (20–47%).

Scheme 48 InCl$_3$-catalyzed synthesis
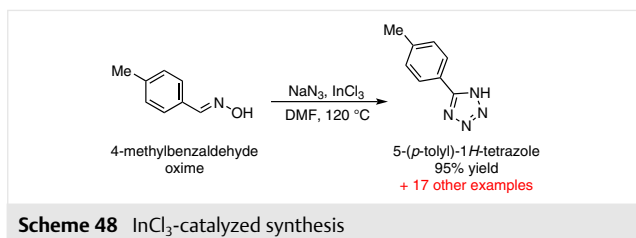
The synthesis of 5-substituted 1H-tetrazoles via the [3+2]-cycloaddition reaction between aliphatic and aromatic nitriles and sodium azide using three Pb(II) salts, viz. PbCl$_2$, Pb(NO$_3$)$_2$, and Pb(OAc)$_2$ was examined by Agarwal and co-workers (Scheme 49).[94] PbCl$_2$ was the most efficient catalyst and gave moderate yields (73–83%) of tetrazoles in 8–14 hours.

Scheme 49 Pb(II) salt catalyzed synthesis

Diphenyl phosphorazidate was used as a reagent for the synthesis of 5-substituted 1H-tetrazoles in good to excellent yields (80–93%) from aldoximes in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene as base in toluene under reflux for 16 hours by Matsugi and co-workers (Scheme 50).[95] 5-Aryl- and 5-heteroaryl-1H-tetrazoles were obtained in higher yields than 5-alkyl-1H-tetrazoles.
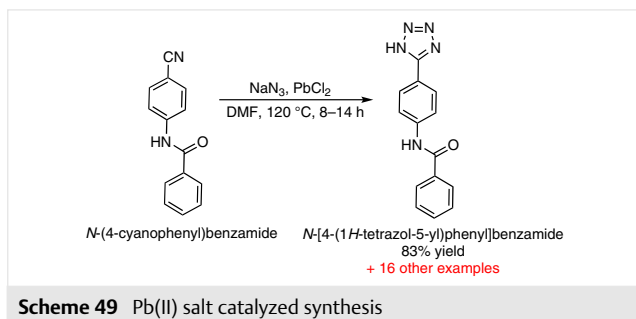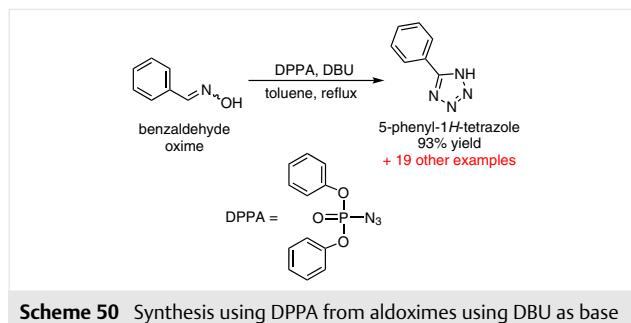
Scheme 50 Synthesis using DPPA from aldoximes using DBU as base

The physical and chemical properties of deep eutectic solvents (DES) are similar to ionic liquids in terms of low vapor pressure, non-volatility, high thermal stability, and recyclability. Compared to ionic liquids, deep eutectic solvents are inexpensive, they have low toxicity, and they are biodegradable. Padvi and Dalal[96] reported an environment friendly procedure for the synthesis of 5-substituted 1H-tetrazoles in the presence of a choline chloride/zinc chloride based deep eutectic solvent at 140 °C (Scheme 51). The 5-substituted 1H-tetrazoles were obtained in good to excellent yields (76–94%).

Scheme 51 Synthesis in choline chloride/zinc chloride based deep eutectic solvent
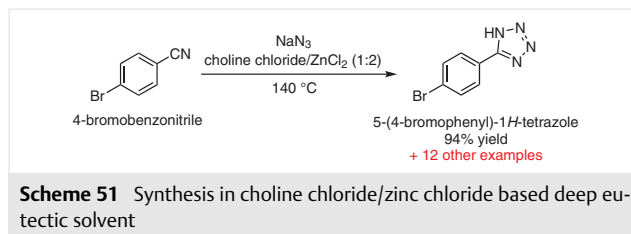
Diisopropylethylammonium acetate (DIPEAc) was used by Mane and co-workers[97] as a reaction medium and catalyst at 80 °C for the [3+2]-cycloaddition reaction of nitriles and sodium azide to give 5-substituted 1H-tetrazoles in up to 94% yields (Scheme 52). The catalyst could be recycled up to four times without significant loss in its catalytic activity.

Scheme 52 Synthesis using DIPEAc as reaction medium and catalyst
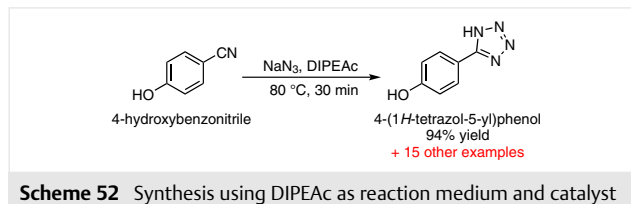
The [3+2]-cycloaddition reaction between nitriles and sodium azide in the presence of urea and acetic acid for 3–20 hours to give various 5-substituted 1H-tetrazoles in high yields (60–95%) was reported by Bandichhor and co-workers (Scheme 53).[98] Mechanistically it is proposed that the reaction occurs via in situ formation of a urea azide active complex (Scheme 54).

Scheme 53 Synthesis in presence of urea and acetic acid
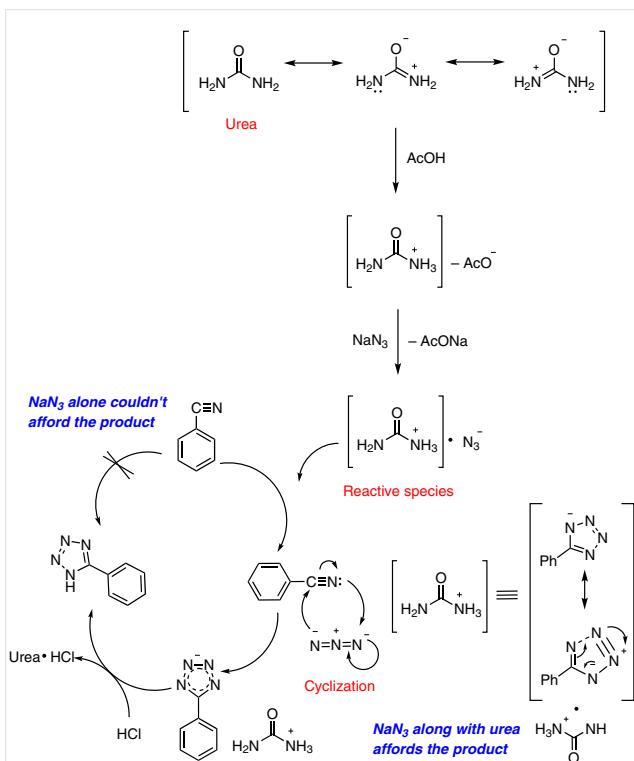
Scheme 54 Proposed mechanism for the synthesis of tetrazoles

Scheme 55 Proline-catalyzed synthesis

Scheme 56 Synthesis using choline azide under catalyst-free and solvent-free conditions

4 Sartans: A Class of Tetrazole-Based Commercial Drugs

Sartans are angiotensin II receptor antagonists or blockers (ARBs) that are used for the treatment of hypertension, congestive heart failure, and myocardial infarct.[101] Losartan was the first non-peptidic ARB to be introduced for the treatment of hypertension in the 1980s.[102] Since then several members of the sartan family have been used as therapeutics for hypertension. Currently, valsartan (brand name, Diovan) holds the maximum popularity as a remedial for hypertension due to its superior efficacy, tolerability and patient compliance.[103] Among several protocols reported in the literature for the synthesis of valsartan,[104] the recovery of organotin reagents, unreacted azide, cumbersome work-up procedures, and lower yields do not qualify them for industrial application. In recent years, several modified routes have been reported where these issues have been addressed to some level.[105] Wang and co-workers[105c] reported the synthesis of valsartan involving recovery of tributyltin chloride via tributyltin fluoride by treatment with sodium fluoride. This improved route also has a setback, that is, on treatment with hydrochloric acid unreacted azide would yield hydrazoic acid, which is highly toxic and explosive in nature. One report in the literature suggested basic hydro-

L-Proline was reported by Bhagat and Telvekar as a catalyst with diverse applicability for the reaction of organic nitriles, thiocyanates, and cyanamides with sodium azide in 1–2 hours to give 5-substituted 1*H*-tetrazoles (Scheme 55).[99] Good to excellent yields (71–96%) were obtained for 5-aryl-, 5-heteroaryl-, and 5-alkyl-1*H*-tetrazoles, 5-(phenylthio) and 5-(benzylthio)-1*H*-tetrazole were obtained in 87% and 93% yield, respectively, and 5-aryl-1-amino-1*H*-tetrazoles were obtained in good yields (81–91%).
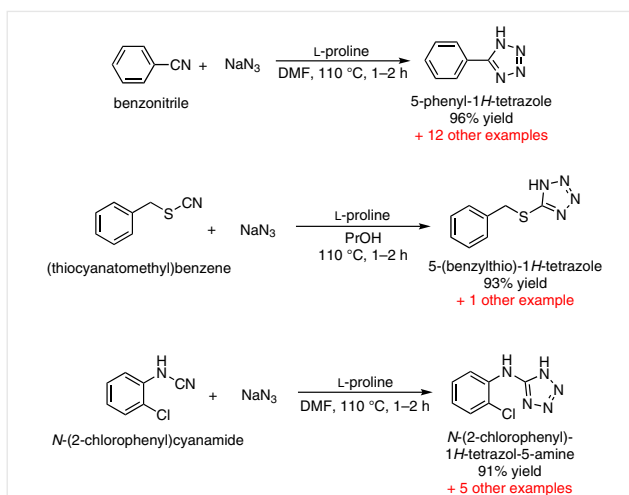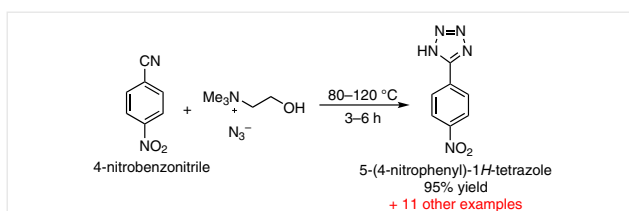
A catalyst-free and solvent-free synthesis of 5-substituted 1*H*-tetrazoles in good to excellent yields (75–95%) from nitriles using a new azidation reagent and the ionic liquid choline azide for 3–6 hours was reported by Heydari and co-workers (Scheme 56).[100] Choline azide is an effective, green, and safe azide source that can be recycled and reused for further tetrazole syntheses. The maximum yield was achieved when 4-nitrobenzonitrile was used.

lysis with sodium hydroxide, which would generate tributyltin hydroxide and sodium azide. Sodium azide can be decomposed by heating, thus releasing nitrogen gas. Moreover, tributyltin hydroxide could be recycled into tributyltin chloride to generate tetrazole.[103] Azide removal to stop the generation of hydrazoic acid is an important issue that needs attention. The generation of hydrazoic acid can be avoided by maintaining basic conditions which can be attained by using triethylamine hydrochloride as a buffer. This results in the formation of thermally stable triethylammonium azide, also environmental concerns could be taken care of by incinerating wastewater.[106] The changes in the production protocols of the active pharmaceutical agent (API) valsartan have led to the contamination of valsartan-containing drugs. The contaminant was found to be *N*-nitrosodimethylamine (NDMA). In a patent by Zheijing Huahai Pharmaceutical,[107] tetrazole formation was reported using anhydrous zinc chloride and sodium azide in aprotic polar solvents like DMF, followed by quenching with sodium nitrite. The reason suspected for the contamination was that the finite stability of DMF might have led to the formation of traces of dimethylamine, subsequently leading to the formation of *N*-nitrosodimethylamine.[101] *N*-Nitrosodimethylamine is a potent carcinogen (WHO/IARC group 2 A, EPA group B2)[108–110] and toxic agent.[111–113] In July 2018, several batches of valsartan were recalled and the research regarding the prevention and causes of contamination are still underway.

5 Conclusions

Tetrazoles, especially 5-substituted 1*H*-tetrazoles have been extensively studied because of their isosteric nature to carboxylic acids, resistance to metabolic degradations, and other characteristics that make them one of the premium classes of heterocycles to be used in medicinal chemistry. Over the years, researchers have overcome various issues such as those related to the use of highly volatile, toxic, and explosive hydrazoic acid as a reactant, longer reaction times, and lower yields. Several methods have been discussed where the reaction time was as short as 10 minutes. Also, yields up to 99% have been reported by several research groups. Some of the protocols listed above have reported the use of highly toxic chemicals like DBU, DPPA, tributyltin chloride, etc. for the synthesis of 5-substituted 1*H*-tetrazoles. From the viewpoint of safety and environmental concerns, this issue requires immediate attention. An outlook is required to develop efficient synthetic methods that are environment friendly. Some existing protocols have reported the use of greener solvents, like water, isopropyl alcohol, and PEG, as a medium of synthesis. The actual concerns lie in the fact that after the workup, these benign solvents end up containing highly toxic azide salts and residual transition metal impurities that are ultimately disposed of in the environment. Consequently, the use of greener solvent, does not make the protocol environment-friendly after all. Some measures that have been undertaken to address the issues of removal of unreacted azide and highly toxic organotin reagents have also been discussed, but they also have certain drawbacks. Therefore, the future prospects in the field of the synthesis of 5-substituted 1*H*-tetrazoles rely on the development of efficient synthetic protocols that can address the issues raised above keeping environmental concerns as a priority.

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