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Recent advances in multicomponent synthesis of 5-substituted 1*H*-tetrazoles from aldehydes: catalytic methods and green chemistry approaches

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This review offers a comprehensive overview of recent advancements (2003–2025) in the synthesis of 5-substituted 1*H*-tetrazoles using aldehyde-based multicomponent reactions (MCRs). It highlights a strategic shift from traditional nitrile–azide cycloadditions to more sustainable and cost-effective procedures. We focus on the design and performance of diverse catalysts, including transition-metal complexes, magnetic nanomaterials, ionic liquids, and sustainable biomass-derived platforms. Furthermore, we explore the distinct mechanistic pathways, such as the oxime- and nitrile-mediated routes, and critically discuss how electronic and steric effects influence reactivity and selectivity of constructing these valuable nitrogen-rich heterocycle. The review also underscores how catalyst innovations have improved atom economy, functional group tolerance, recyclability, and environmental compatibility. By consolidating these developments, this work not only showcases the versatility of aldehyde-based MCR strategies but also provides a roadmap for future research toward scalable and industrially relevant tetrazole synthesis.

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1. Introduction

Tetrazoles, a unique class of heterocyclic compounds, have a wide range of applications due to their distinctive five-membered ring structure with four nitrogen atoms.¹ These synthetic compounds, not found in nature, are particularly important in medicinal chemistry, where they serve as

bioisosteres for the carboxylic acid group. This characteristic is leveraged in the development of drugs like valsartan and losartan, which are used to treat high blood pressure. Their use in drugs is attributed to the improved metabolic stability and bioavailability that the tetrazole ring provides.² The tetrazole ring's structure allows for tautomerism, a type of isomerism where compounds exist in an equilibrium of two or more forms that can interconvert by a simple migration of an atom or group. In unsubstituted tetrazole, two main tautomers exist: 1*H*-tetrazole and 2*H*-tetrazole (Scheme 1). The position of the proton on one of the nitrogen atoms in the ring determines which tautomer is present. The 1*H*-tautomer has the hydrogen atom at the N1 position, while the 2*H*-tautomer has the hydrogen at the N2 position. In solution, these two forms are in a dynamic equilibrium, with the specific ratio depending on the solvent, temperature, and substituents on the ring. The tautomeric state of tetrazole derivatives is a critical factor influencing their

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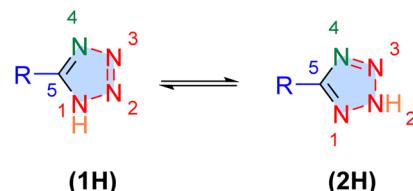
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Scheme 1 Tautomerism of tetrazole derivatives.



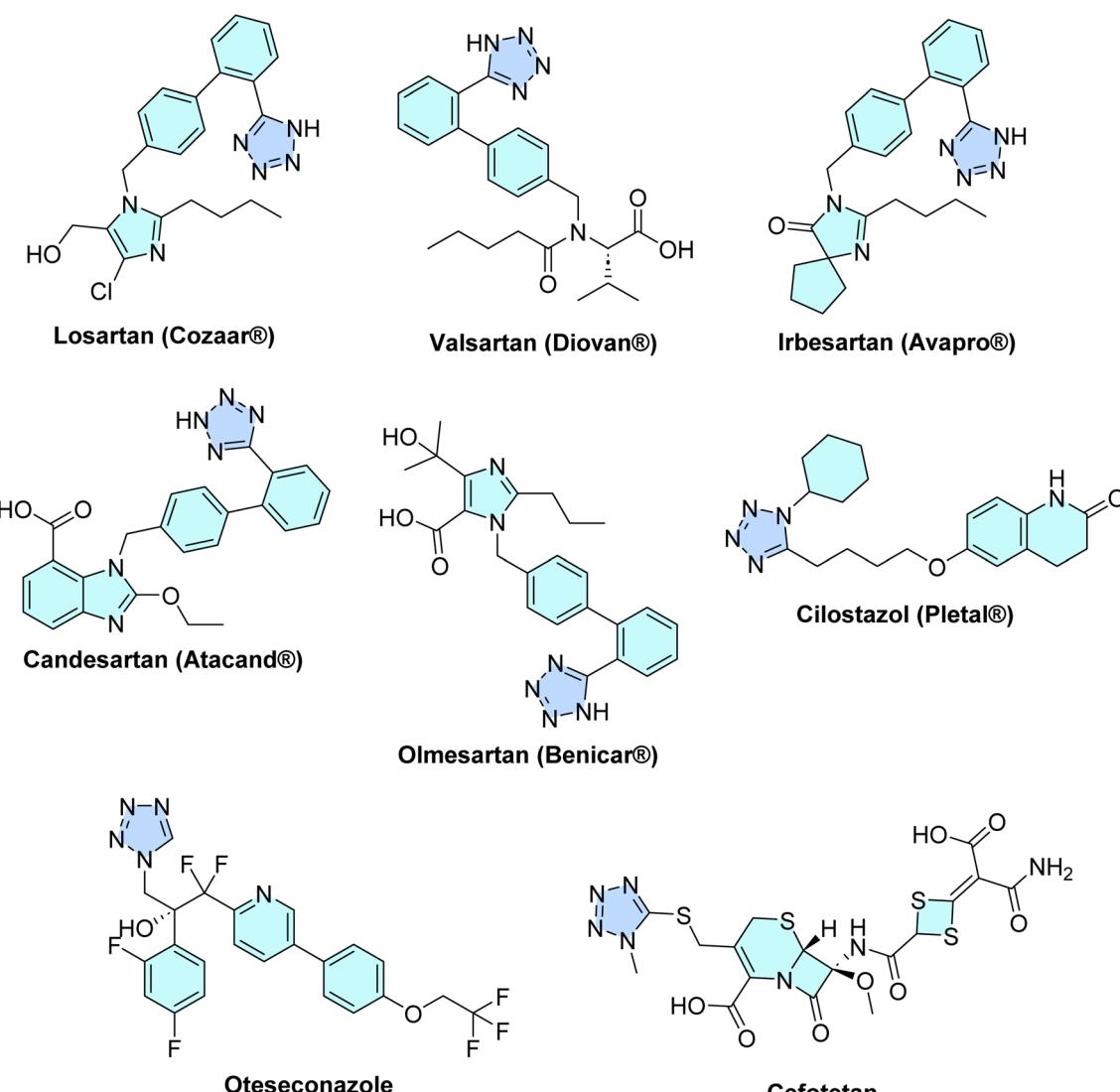
physical and chemical properties, including their acidity and biological activity.^{1,2}

Beyond their medicinal uses, tetrazoles are also valuable as energetic materials because of their high nitrogen content and thermal stability.³ This makes them suitable for use in explosives, propellants, and rocket fuels.⁴⁻⁶ Furthermore, tetrazoles find applications in coordinating ligands and pharmaceutical intermediates (Scheme 2).⁷⁻⁹

The global tetrazole market is experiencing steady, derivative-specific growth, primarily driven by pharmaceutical, agrochemical, and specialty chemical applications. The 1*H*-methyl-1*H*-tetrazole market was valued at ~US\$7.1 million in 2024 and is expected to reach US\$7.6 million by 2031 (CAGR ≈ 1.0%), with Asia-Pacific supplying most of the production.¹⁰ The 1*H*-tetrazole-1-acetic acid derivative serves as a key intermediate in cephalosporin antibiotics,¹¹ while other specialized derivatives, such as 5-amino-1-methyl-1*H*-tetrazole¹² and 5-ethylthio-1*H*-tetrazole,¹³ are widely used in chemical reagents, medicinal chemistry, and pesticide intermediates. Additional niche

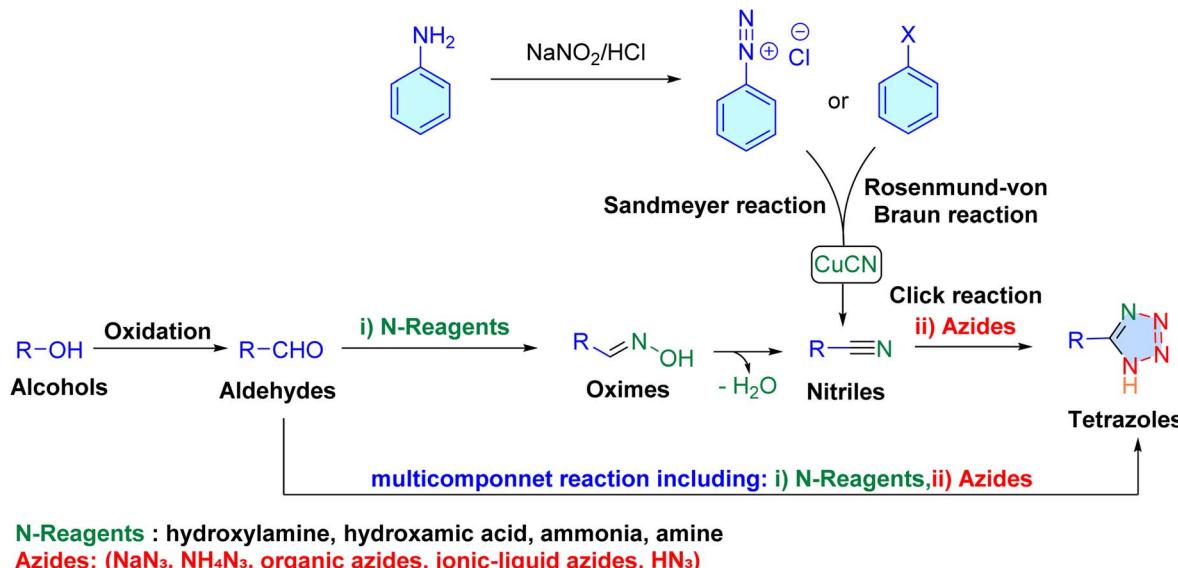
tetrazoles, including 5-(4-chlorobutyl)-1-cyclohexanyl-tetrazole¹³ and 5-(2-bromophenyl)-1*H*-tetrazole,¹⁴ highlight the diversity of applications and supplier ecosystems. Overall, pharmaceutical intermediates dominate the market, and Asia-Pacific, particularly China, remains the leading producer, reflecting strong demand across drug development, agrochemical formulations, and advanced materials.

The classical and widely-studied method for synthesizing 5-substituted 1*H*-tetrazoles relies on the [3 + 2] cycloaddition of nitriles with azides, serves as a foundational method.¹⁵⁻¹⁷ This route, however, faces significant drawbacks, including the high cost of nitrile starting materials, the need for expensive catalysts such as palladium,¹⁸ gold¹⁹ and silver²⁰ under harsh reaction conditions, and safety concerns associated with handling hazardous azide reagents. To obtain the necessary nitriles, chemists have traditionally relied on multi-step procedures such as the Sandmeyer and Rosenmund-von Braun reactions from aromatic amines, or a sequence of oxidation and dehydration steps from alcohols and aldehydes.²¹⁻²⁷ These stepwise



Scheme 2 Selected examples of bioactive tetrazole derivatives.





Scheme 3 Summary of the classical method for synthesizing 5-substituted 1*H*-tetrazoles.

syntheses are often inefficient, requiring multiple purifications and leading to low overall yields, which limits their broad practical application (Scheme 3).

In contrast, modern methodologies have shifted towards a more efficient one-pot multicomponent reaction (MCR) approach. This streamlined process directly synthesizes tetrazoles from readily available and inexpensive aldehydes in a single reaction vessel, *via* the *in situ* formation and conversion of oximes and/or nitriles and their conversion to tetrazoles (Scheme 3).^{28,29} This modern method is highly advantageous because it eliminates lengthy stepwise sequences and multiple purification steps. By improving atom economy, the efficiency with which atoms from the starting materials are incorporated into the final product, and minimizing waste, this approach is far more practical and superior to traditional methods for the synthesis of tetrazoles.

Building upon these advancements, numerous studies have explored the one-pot synthesis of tetrazoles from aldehydes. While numerous review articles explore the general applications and broader synthesis of tetrazoles,^{2,30-33} a specific and comprehensive review focusing exclusively on the catalytic synthesis of tetrazoles from aldehydes is, to our knowledge, currently unavailable. Therefore, this article aims to fill this gap by providing a detailed overview of the various catalytic strategies that have been developed for this highly efficient and practical transformation. We will highlight key methodologies, discuss their advantages and limitations, and offer insights into future research directions in this important field.

2. Chemical methodologies in synthesis of 5-substituted 1*H*-tetrazoles from aldehydes

2.1. Transition metals-catalyzed methods

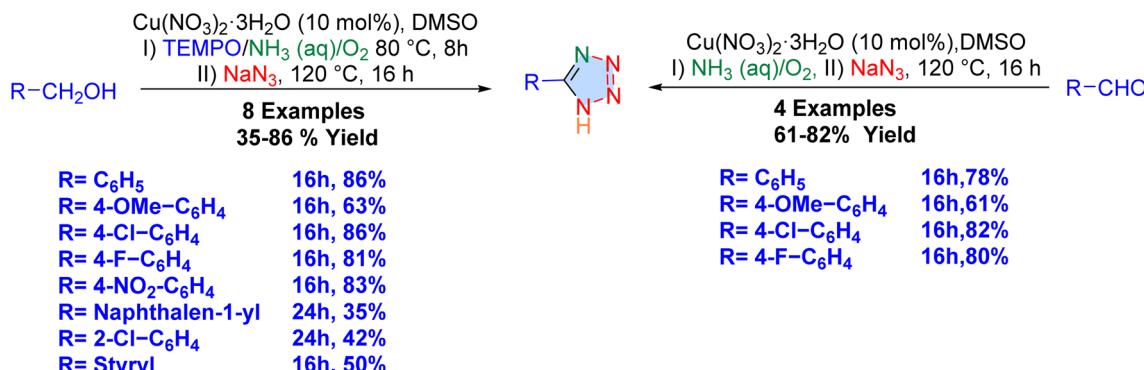
Transition metal-catalyzed methods have recently emerged as a highly attractive and efficient approach for tetrazole synthesis.

While traditional synthetic routes using nitriles and azides often require expensive noble metal catalysts like palladium,¹⁸ gold,¹⁹ platinum³⁴ and silver²⁰ the advent of modern multicomponent one-pot reactions using aldehydes has enabled a significant shift toward more sustainable and cost-effective alternatives. These new methodologies effectively utilize a range of earth-abundant and eco-friendly metals, including copper,³⁵ titanium,³⁶ lanthanum,³⁷ ruthenium,³⁸ cobalt,³⁹ tin,⁴⁰ bismuth,⁴¹ zinc and iron.⁴² Among these, copper-based catalysts have garnered particular attention due to their remarkable efficiency, versatility, and low cost, positioning them as a central focus of modern research in tetrazole synthesis.

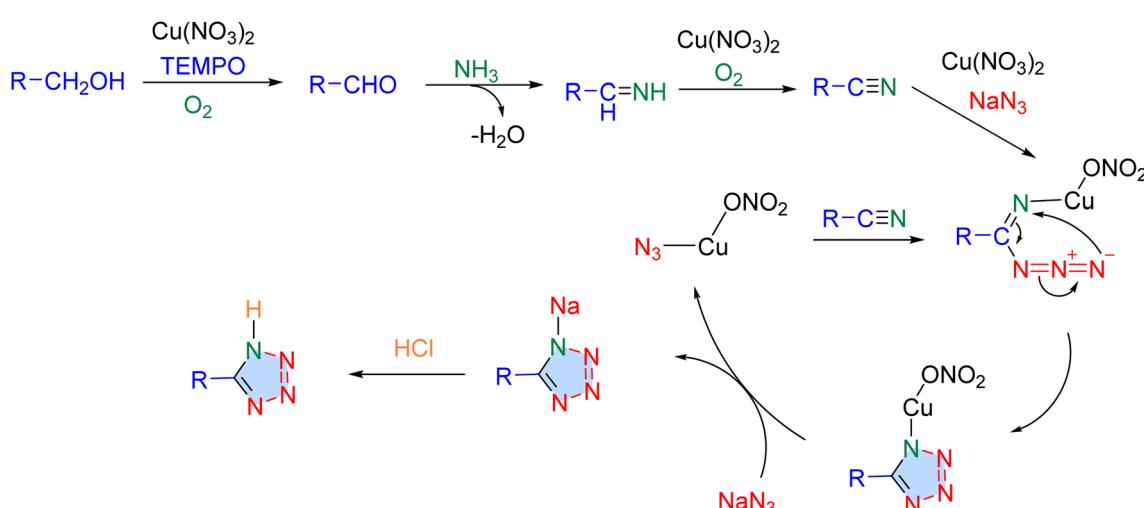
2.1.1. Catalytic systems based on copper. Copper is one of the most versatile and Earth-abundant transition metals, highly regarded for its catalytic efficiency, tunable redox properties, and superior cost-effectiveness compared to noble metals.²³ Leveraging these advantageous features, a wide range of structurally diverse copper-based catalytic systems including; simple salts, coordination complexes, and supported species have been developed for this special transformation. These catalysts have been effectively anchored onto diverse supports such as silica, polymers, carbon materials, and magnetic nanoparticles to enhance performance and recyclability. In this section, we summarize these reported copper-based catalysts, focusing specifically on their structural diversity, catalytic performance, and mechanistic insights.

2.1.1.1. Salts and complexes of Cu. In 2016, Tao and coworkers reported a practical and efficient copper nitrate-catalyzed one-pot protocol for the direct synthesis of 5-substituted 1*H*-tetrazoles from benzylic alcohols or aldehydes using ammonia and sodium azide as nitrogen sources in DMSO (Scheme 4).⁴³ The reaction pathway for alcohols involved an initial oxidation step using TEMPO, aqueous NH₃, and oxygen at 80 °C for 8 h, followed by [3 + 2] cycloaddition with NaN₃ at 120 °C for 16 h (Scheme 5). For aldehydes, the oxidation step was omitted, and the same conditions were applied. Electron-





Scheme 4. $\text{Cu}(\text{NO}_2)_2 \cdot 3\text{H}_2\text{O}$ catalyzed the synthesis of 5-substituted 1*H*-tetrazoles from aldehydes and alcohols.

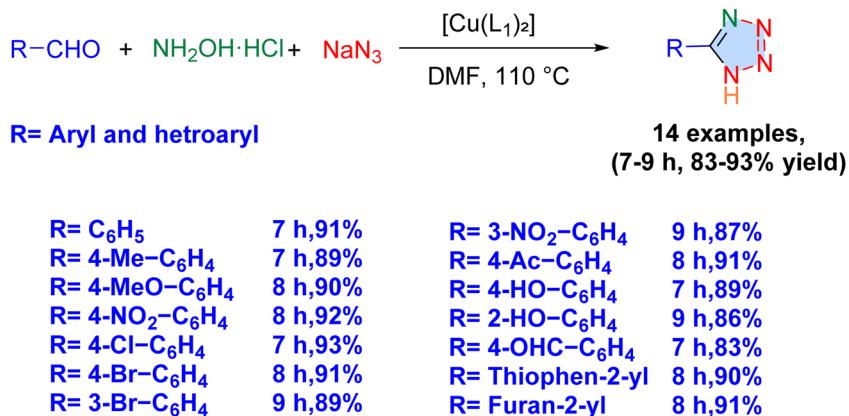
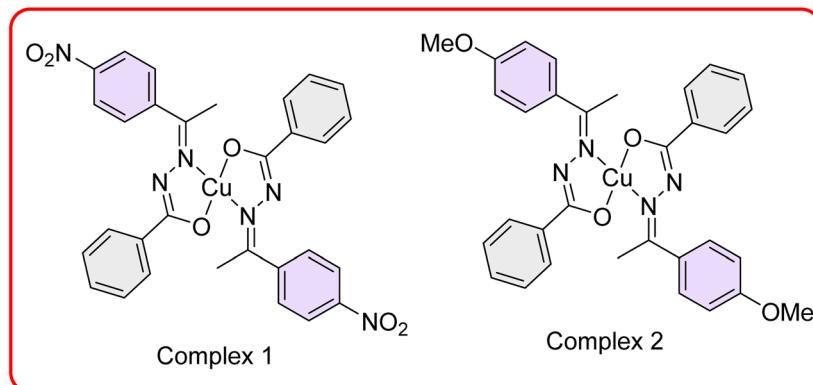


Scheme 5 Proposed mechanism for $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ catalyzed the synthesis of 5-substituted 1*H*-tetrazoles from aldehydes and alcohols.

withdrawing substituents enhanced reactivity and yields, while electron-donating groups gave moderate results. Steric hindrance at the *ortho*-position or bulky groups significantly lowered yields. Direct comparison of identical substrates revealed that alcohols generally gave slightly higher yields (e.g., 86% for 5-phenyl-1*H*-tetrazole from benzyl alcohol *versus* 78% from benzaldehyde) but aldehydes offered shorter overall preparation times by bypassing the initial oxidation stage. This homogeneous system combines operational simplicity, cost-effectiveness, and broad substrate scope, with alcohols offering slightly higher yields but aldehydes enabling more time-efficient synthesis.

In 2019, Layek and colleagues described the synthesis of two benzoylhydrazine Schiff base-ligated copper(II) complexes, $[\text{Cu}(\text{L}_1)_2]$ and $[\text{Cu}(\text{L}_2)_2]$, and their catalytic application in the preparation of 5-substituted $1H$ -tetrazoles *via* a three-component reaction of aldehydes, hydroxylamine hydrochloride, and sodium azide (Scheme 6).⁴⁴ Single-crystal X-ray analysis revealed distorted square-planar geometries around Cu(II), with the electronic nature of the ligands strongly influencing activity. Complex **1**, containing a nitro-substituted ligand, was more Lewis acidic and exhibited higher catalytic efficiency than

complex 2 which is due to the N,O-donor Schiff base ligands that increases the Lewis acidity and stability of the copper(II) catalysts and facilitate the reactions smoothly. Optimal conditions employed only 0.5 mol% catalyst in DMF at 110 °C, affording tetrazoles in up to 93% yield. Substrate scope studies revealed significant electronic and steric effects. Aldehydes bearing electron-withdrawing substituents (NO₂, Br, COCH₃) gave higher yields than those with electron-donating groups (OCH₃, OH), while *ortho*-substitution reduced reactivity compared with *meta*- or *para*-isomers. Importantly, heteroaromatic aldehydes such as furfural and thiophene carboxaldehyde also participated smoothly, underscoring the versatility of the system. A key result is the chemoselectivity mono-tetrazole formation from terephthalaldehyde as a bifunctional substrate, demonstrating the system's control over multi-functional substrates. Mechanistic studies support a pathway where the copper center activates the aldehyde, enabling oxime formation with hydroxylamine. Subsequent dehydration generates a nitrile intermediate, which undergoes [3 + 2] cycloaddition with azide to deliver the tetrazole product (Scheme 7). The identification of the nitrile as the crucial intermediate highlights the mechanistic similarity to classical

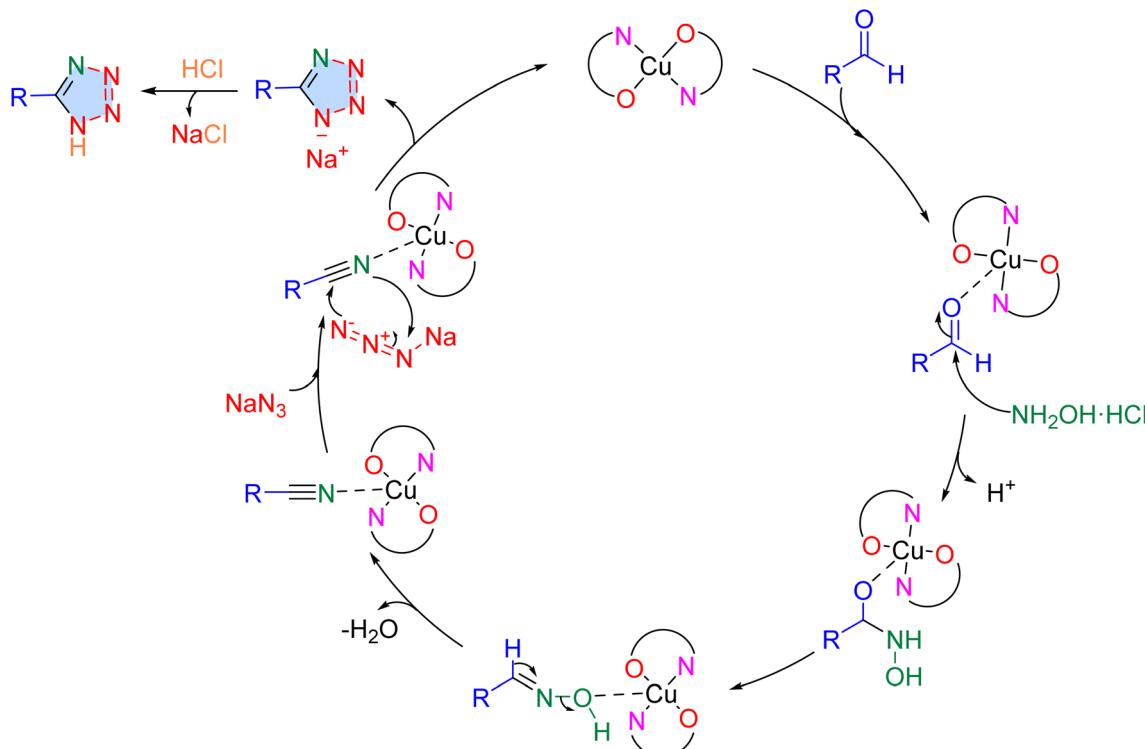


Scheme 6 Copper(II) benzoylhydrazine Schiff base complex catalyzed the cyclo-condensation of aldehydes, hydroxylamine and sodium azide.

nitrile–azide cycloadditions, but with the significant advantage of directly utilizing aldehydes.

In 2019, Xiong and co-workers reported a practical and green protocol for the synthesis of 5-substituted-1*H*-tetrazoles *via* a one-pot three-component condensation of aldehydes, hydroxylamine hydrochloride, and sodium azide using Cu(OAc)₂ (20 mol%) as the catalyst in a choline chloride–urea deep eutectic solvent (DES) at 100 °C for 12 h (Scheme 8).⁴⁵ The method afforded moderate to excellent yields (68–90%) and proved efficient on a multi-gram scale, highlighting its synthetic utility. The DES medium not only offers a biodegradable and inexpensive alternative to toxic, high-boiling solvents but also suppresses the formation of volatile HN₃, thereby improving safety and environmental compatibility. Electronic effects of substituents on aromatic aldehydes were well tolerated: both electron-donating and electron-withdrawing groups afforded good conversions. Sterically hindered and heteroaromatic aldehydes (*e.g.*, pyridyl, furyl) also underwent smooth transformations, underlining the broad substrate scope. The plausible mechanism involves initial oxime formation from the aldehyde and hydroxylamine, followed by Cu(II)-assisted activation of the C=N bond, which undergoes [3 + 2] cycloaddition with azide to yield the tetrazole. This protocol combines operational simplicity, scalability, and high atom economy with the advantages of DES as a sustainable solvent. Overall, it represents a significant advance in the environmentally benign synthesis of pharmacologically relevant tetrazoles.

Gayathri *et al.* reported the design and catalytic application of novel copper(I) complexes $[\text{Cu}(\text{PPh}_3)_2(\text{L}_{1-3})]$, where heteroaromatic hydrazone Schiff bases act as bidentate N'N ligands (Scheme 9).⁴⁶ Single-crystal XRD confirmed a distorted tetrahedral geometry around Cu(I), with stabilization influenced by electronic effects of the heteroaryl ligands. These complexes were prepared by direct reaction of $[\text{Cu}(\text{PPh}_3)_2(\text{CH}_3\text{COO})]$ with pre-synthesized hydrazone ligands, and characterized comprehensively by FT-IR, UV-Vis, NMR, ESI-MS, and DFT studies. Among the catalysts, complex 1 (benzothiazole-based) displayed the highest activity, attributable to favorable steric compactness and electronic stabilization, outperforming quinoline- (2) and nicotinic acid-based (3) analogues. Catalytic tests in three-component reactions of aldehydes, hydroxylamine hydrochloride, and sodium azide in DMF revealed efficient synthesis of 5-substituted 1*H*-tetrazoles under mild conditions (1 mol% catalyst, 100 °C, 12 h, O₂ atmosphere), with yields up to 96%. Substrate scope studies showed that aryl aldehydes bearing electron-withdrawing substituents gave slightly higher yields than electron-donating substituents, consistent with enhanced electrophilicity at the carbonyl center. Alkyl aldehydes afforded only moderate yields, while heteroaryl and fused aryl substrates performed comparably well. The plausible mechanism proceeds *via* *in situ* oxime formation, dehydration to nitrile, followed by [3 + 2] cycloaddition with azide. This work highlights how steric/electronic ligand design modulates Cu(I) catalysis, offering low catalyst loading, high efficiency, and

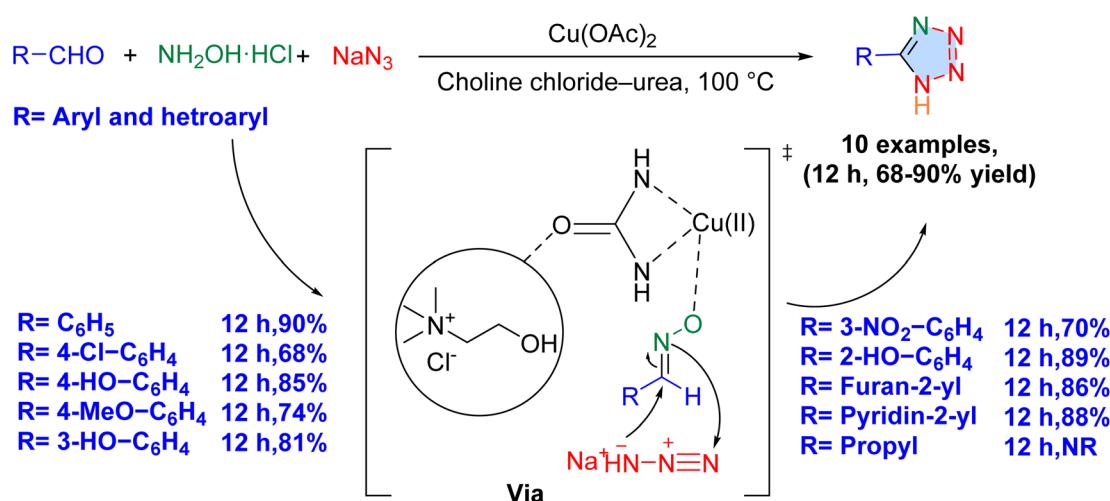


Scheme 7 The plausible mechanism for copper(II) benzoylhydrazine Schiff base complex catalyzed the synthesis of 5-substituted 1*H*-tetrazoles from aldehydes, hydroxylamine and sodium azide.

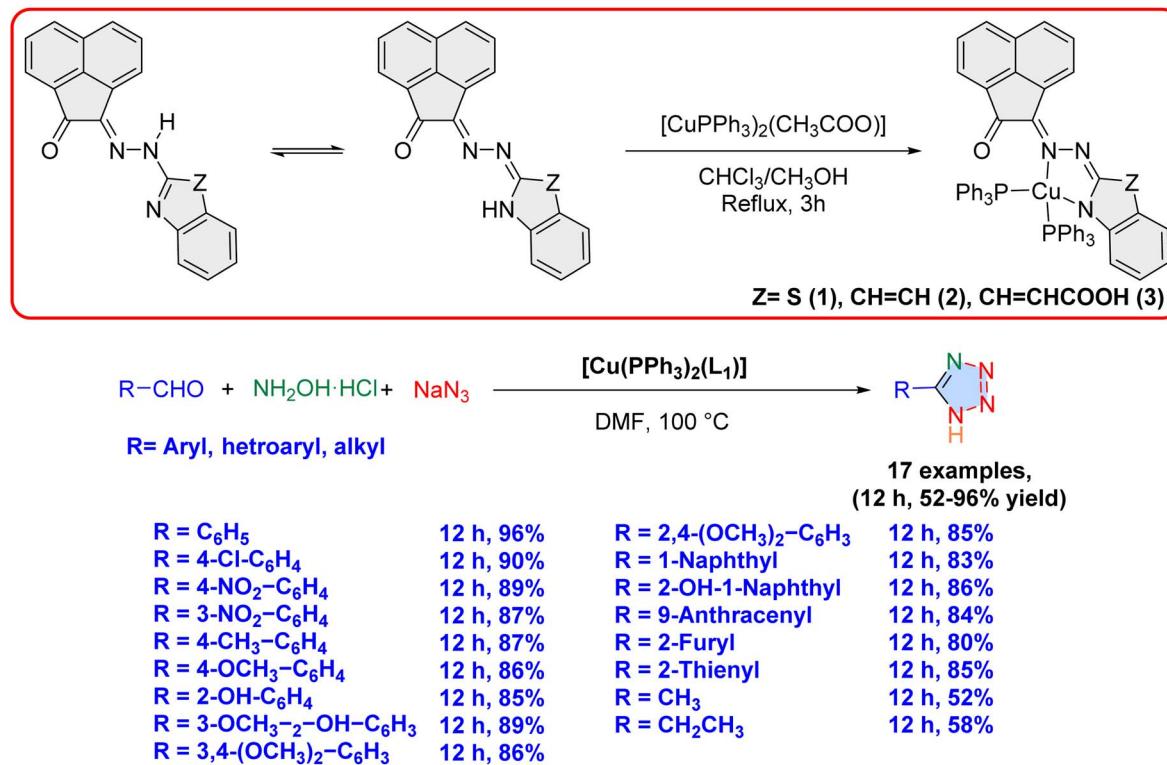
broad substrate tolerance, positioning these complexes as promising candidates for sustainable tetrazole synthesis.

2.1.1.2. *Cu/SiO₂*. In 2015, Abdollahi-Alibeik and Moaddeli reported a novel and efficient multicomponent strategy for the synthesis of 5-substituted 1*H*-tetrazoles using the condensation of various aldehydes, hydroxylamine, and sodium azide catalyzed by Cu-MCM-41 nanoparticles in DMF at 140 °C.³⁵ This method offers a practical alternative to traditional nitrile-azide cycloaddition by employing readily available aldehydes and

their *in situ* conversion to oximes intermediates with a heterogeneous, recyclable catalyst. The Cu-MCM-41 catalyst, particularly with a Cu/Si molar ratio of 0.05, demonstrated optimal activity, attributed to the high dispersion of copper sites and the strong Lewis acidity facilitating the reaction. This protocol demonstrated broad substrate scope for aromatic and heteroaromatic aldehydes, where electron-donating substituents promoted higher yields and faster reaction rates, while steric hindrance, particularly in *ortho*-substituted aldehydes, led to



Scheme 8 Copper(II) acetate catalyzed one-pot synthesis of 5-substituted 1*H*-tetrazoles in choline chloride-urea solvent.



Scheme 9 Copper(i)-benzothiazole hydrazone complex catalyzed the synthesis of 5-substituted 1*H*-tetrazoles.

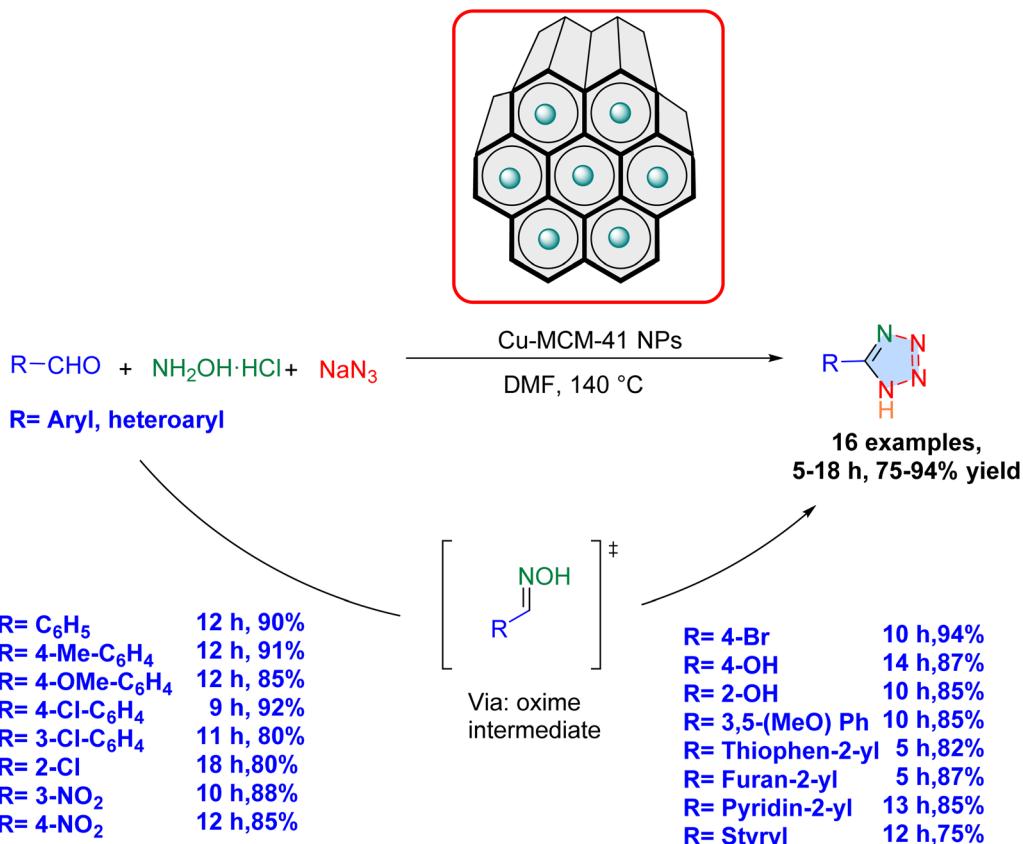
prolonged reaction times, indicating a substrate electronic effect on the oxime formation and cycloaddition step (Scheme 10). However, the methodology still requires relatively high temperatures (140 °C) and employs DMF as solvent, which may limit its environmental impact profile. Catalyst reusability was moderate, maintaining significant activity over three cycles, though slight copper leaching and coke deposition were observed. Overall, this work underscores the critical influence of copper loading in tailoring the catalytic properties of mesoporous Cu-MCM-41 and provides a safer and more accessible route to tetrazoles compared to conventional nitrile-azide cycloadditions with simple purification method as the products were precipitated after the acidification of reaction mixture and were crystallized in mixture of water and ethanol.

2.1.1.3. Cu/polymers. In 2016 Kazemnejadi and coworkers reported a highly efficient, environmentally benign approach for the synthesis of 5-substituted 1*H*-tetrazoles using a polyvinyl alcohol immobilized Cu(II) Schiff base complex (PVA@Cu(II) Schiff base complex) as a heterogeneous catalyst under milder conditions (Scheme 11).⁴⁷ The catalyst was synthesized by functionalizing polyvinyl alcohol (PVA) with epichlorohydrin, followed by Schiff base formation using salicylaldehyde and subsequent complexation with Cu(OAc)₂ to yield the PVA@-Cu(II) Schiff base complex. The obtained structure, containing both hydrophilic and lipophilic moieties, promoted the one-pot three-component reaction of various aliphatic and aromatic aldehydes with hydroxylamine hydrochloride and sodium azide in water at room temperature within a very short reaction time (typically under 15 minutes) and in excellent yields (70–98%).

Electronic effects of substituents significantly influenced reactivity: electron-donating and electron-withdrawing groups on aromatic aldehydes were generally well tolerated, while *ortho*-hydroxy groups slightly reduced yields (70–80%) due to possible intramolecular hydrogen bonding and steric hindrance, which may impede coordination to the copper center. Aliphatic aldehydes also performed efficiently, indicating broad substrate scope. This method offers several advantages over previously reported procedures: operation under ambient conditions, use of water as a green solvent, simple work-up, high atom economy, and catalyst recyclability with simple filtration up to five runs with minimal loss of activity. Such features make this protocol a sustainable and cost-effective alternative for tetrazole synthesis, particularly attractive for pharmaceutical and fine chemical applications.

The authors suggested that plausible mechanism involves initial oxime formation from aldehydes and hydroxylamine, followed by a copper-catalyzed [3 + 2] cycloaddition between the oxime and in-situ-generated hydrazoic acid (from the reaction of sodium azide and remaining acidic protons from the hydroxylamine hydrochloride), and subsequent dehydration affording the tetrazole (Scheme 12). The PVA-supported copper complex acts as a microenvironment, enhancing substrate solubility and proximity through hydrogen bonding and coordination, enabling the reaction to proceed without elevated temperature or toxic solvents.

2.1.1.4. Cu/C. Khalifeh *et al.* (2020) reported a practical and efficient Cu/C nanocatalyst for the one-pot three-component synthesis of 5-substituted 1*H*-tetrazoles (Scheme 13).⁴⁸ The

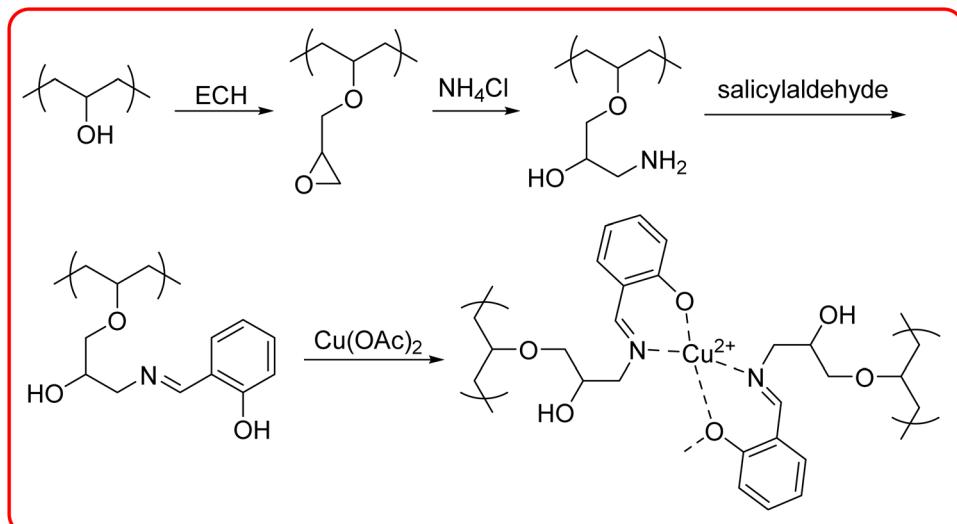


Scheme 10 Copper supported onto the MCM-41 catalyzed the condensation of aldehydes, hydroxylamine and sodium azide.

catalyst was prepared *via* established protocols for copper nanoparticles supported on charcoal, ensuring high surface area and stability. The optimization results indicate that the copper species in Cu/C are essential active sites responsible for the observed catalytic activity and the best performances was obtained using 5 mol% of catalyst based on copper amount. The authors proposed that the reaction plausibly proceeds through oxime → nitrile → azide addition in a sequential manner in DMF at 120 °C to afford the tetrazole derivatives in high yields (74–89%). The methodology tolerated a wide range of substituents, including electron-donating and electron-withdrawing groups. Notably, electronic effects did not significantly alter reactivity, while sterically hindered *ortho*-substituted aldehydes required longer reaction times. Extension to heteroaryl aldehydes such as furfural, thiophene-3-carbaldehyde, and *N*-methylpyrrole-2-carbaldehyde demonstrated the robustness of the system under acid-sensitive conditions. Importantly, the Cu/C catalyst was readily recyclable up to five cycles without loss of efficiency, offering a sustainable route compared to toxic nitrile precursors. Overall, the study highlights Cu/C as a cost-effective, reusable, and high-performing catalyst for tetrazole synthesis.

In 2022, Tahmasbi *et al.* developed a sustainable copper-based magnetic nanocatalyst by anchoring Cu(II) onto magnetic nitrogen-doped carbon (MNC) derived from silk cocoon biomass (Scheme 14).⁴⁹ The preparation involved

thermal carbonization of silk cocoons with KOH activation, deposition of Fe₃O₄ nanoparticles to impart magnetic properties, and subsequent immobilization of Cu(II). Characterizations confirmed the porous nitrogen-doped structure, a copper loading of 3.5 wt%, uniform metal dispersion, high thermal stability, and superparamagnetism that enabled facile catalyst recovery. Catalytic performance was evaluated in the one-pot three-component synthesis of 5-substituted 1*H*-tetrazoles from aldehydes, hydroxylamine hydrochloride, and sodium azide in DMF at 80 °C. Using only 0.26 mol% catalyst, the model benzaldehyde reaction achieved 95% yield in 2.5 h. While the use of a minimal catalyst loading represents a significant achievement, the reaction's efficiency remains directly proportional to the copper concentration. Lower loadings reduced efficiency, but exceeding the optimal concentration offered no additional benefit. Substituent effects were significant: aryl aldehydes with electron-withdrawing groups reacted faster and with higher yields, while electron-donating groups prolonged reaction times due to reduced carbonyl electrophilicity. *Ortho*-Substituted aldehydes displayed steric hindrance, lowering reactivity. Conjugated heteroaryl substrates (indole, pyridine, thiophene) and benzyl/alkyl aldehydes also afforded excellent yields, highlighting the broad scope. The plausible mechanism proceeds *via* oxime formation from aldehydes and hydroxylamine, followed by azide cycloaddition, without nitrile intermediates. The MNC-Cu catalyst demonstrated remarkable



R= Aryl and alkyl

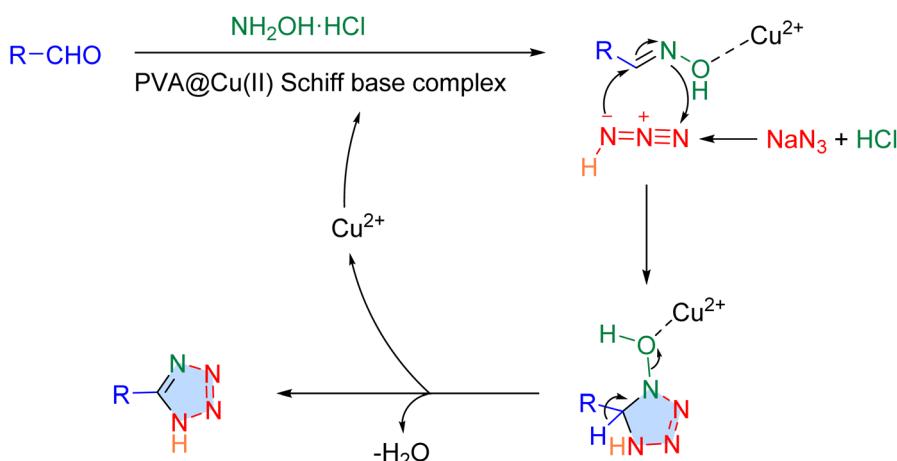
**16 examples,
(3-15 min, 70-98% yield)**

$\text{R= C}_6\text{H}_5$	7 min, 98%	$\text{R= 2-OMe-C}_6\text{H}_4$	5 min, 98%
$\text{R= 4-NMe}_2\text{-C}_6\text{H}_4$	5 min, 98%	$\text{R= 3,4-(OH)}_2\text{-C}_6\text{H}_3$	5 min, 70%
$\text{R= 4-OMe-C}_6\text{H}_4$	7 min, 98%	$\text{R= 4-OH-C}_6\text{H}_4$	7 min, 88%
$\text{R= 4-NO}_2\text{-C}_6\text{H}_4$	15 min, 98%	R= Anthracen-9-yl	8 min, 95%
$\text{R= 3-NO}_2\text{-C}_6\text{H}_4$	15 min, 97%	R= Furan-2-yl	8 min, 98%
R= Indol-3-yl	12 min, 98%	R= 2-Phenylethyl	12 min, 80%
$\text{R= 4-Cl-C}_6\text{H}_4$	7 min, 98%	$\text{R= Naphthalen-2-yl}$	5 min, 95%
$\text{R= 2-OH-C}_6\text{H}_4$	15 min, 80%	R= Hexyl	3 min, 80%

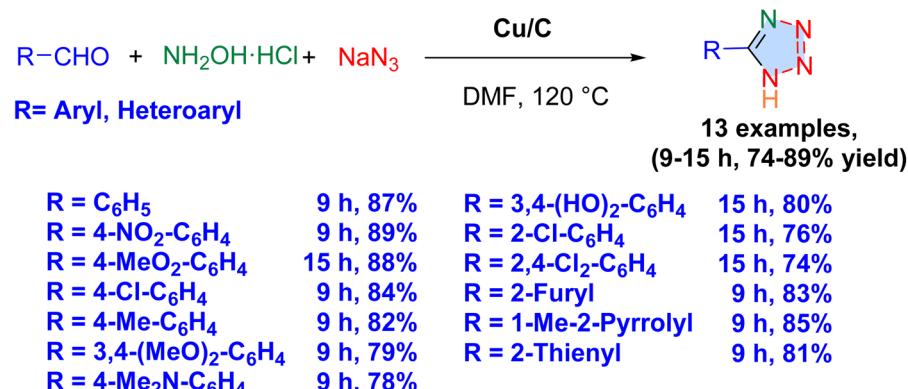
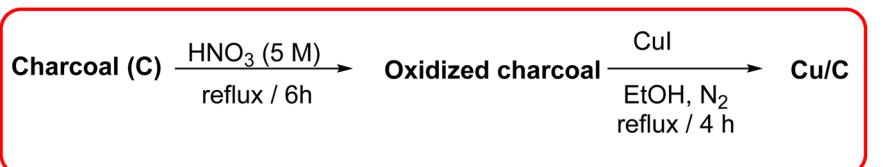
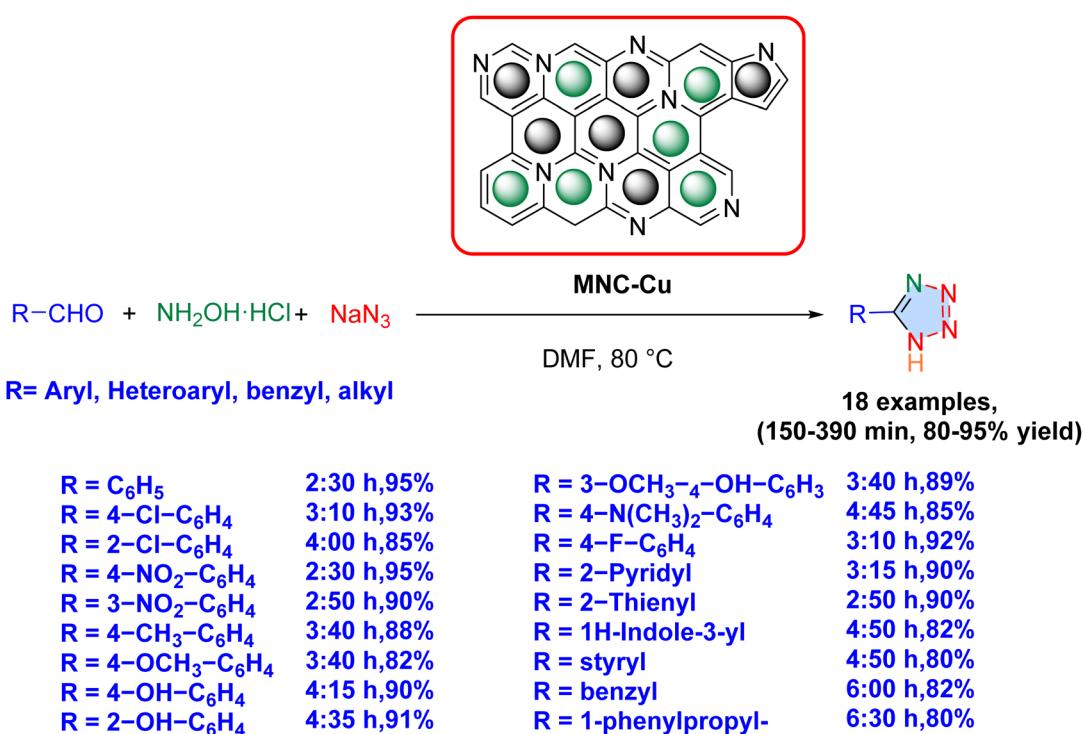
Scheme 11 Polyvinyl alcohol immobilized copper(II) Schiff base complex catalyzed the cyclo-condensation of aldehydes, hydroxylamine and sodium azide.

reusability, retaining activity over five cycles with negligible Cu leaching, attributed to strong metal anchoring and magnetic recoverability. Compared with conventional homogeneous

systems, this biopolymer-derived, magnetically recyclable catalyst operates efficiently under milder conditions, combining sustainability with excellent performance. Its design offers



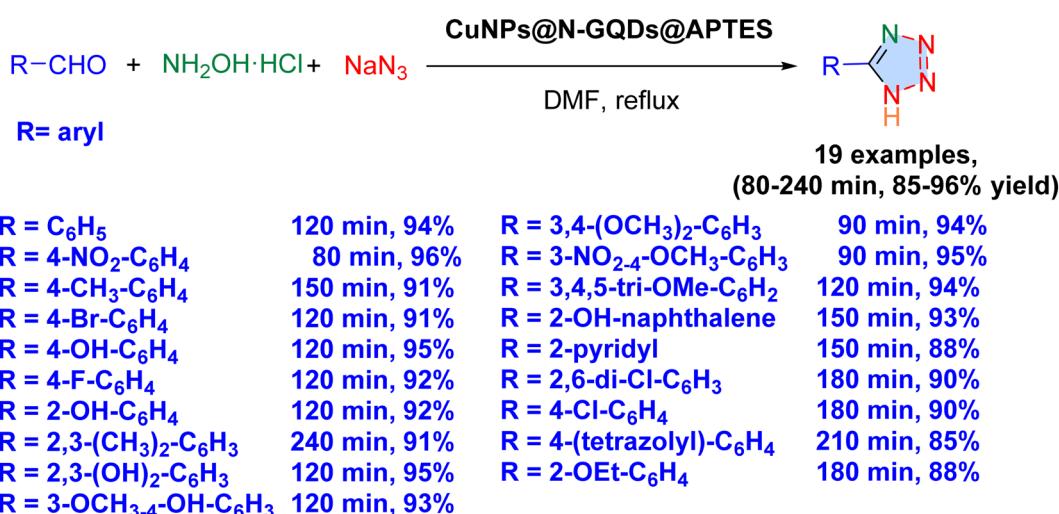
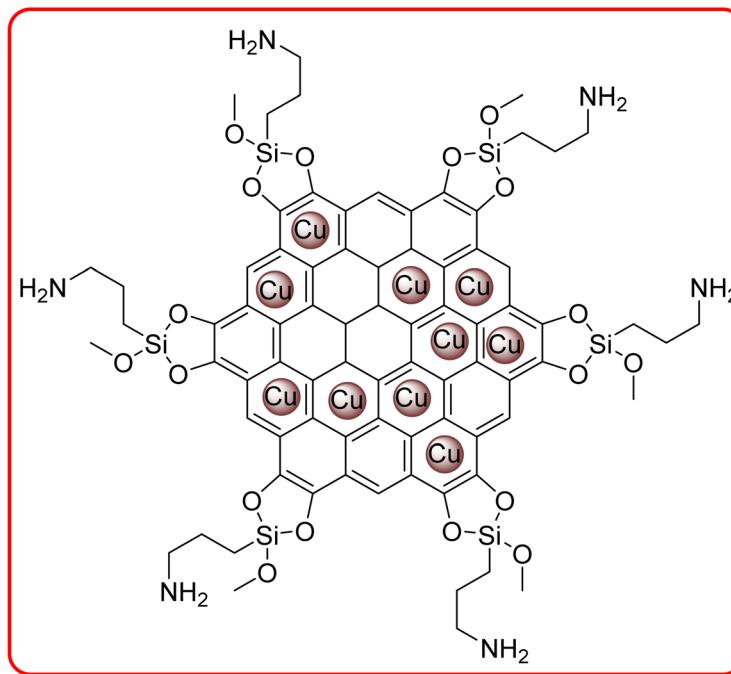
Scheme 12 Plausible mechanism for the formation of 5-substituted 1*H*-tetrazoles using over the catalysis of PVA@Cu(II) Schiff base complex.

Scheme 13 Copper supported on charcoal catalyzed one-pot synthesis of 5-substituted 1*H*-tetrazoles.Scheme 14 Magnetic nitrogen-doped carbon–copper catalyzed one-pot synthesis of 5-substituted 1*H*-tetrazoles.

a green and practical platform for tetrazole synthesis and future catalytic applications.

Base catalysis has long been central to organic transformations, especially in multicomponent reactions, where the choice of catalyst profoundly influences efficiency, selectivity, and sustainability. In this context, Bagade and Kumbhar (2025) report the development of an aminated copper-doped nitrogen quantum dot catalyst immobilized with APTES (CuNPs@N-

GQDs@APTES) as a heterogeneous catalyst for the synthesis of 5-substituted-1*H*-tetrazoles *via* a three-component reaction of aromatic aldehydes, sodium azide, and hydroxylamine hydrochloride in water at room temperature (Scheme 15).⁶² The preparation of the catalyst involves sequential synthesis of CuNPs, integration with nitrogen-doped graphene quantum dots, and surface functionalization with APTES as the basic site to cooperate with copper in catalyzing the process. Reaction was

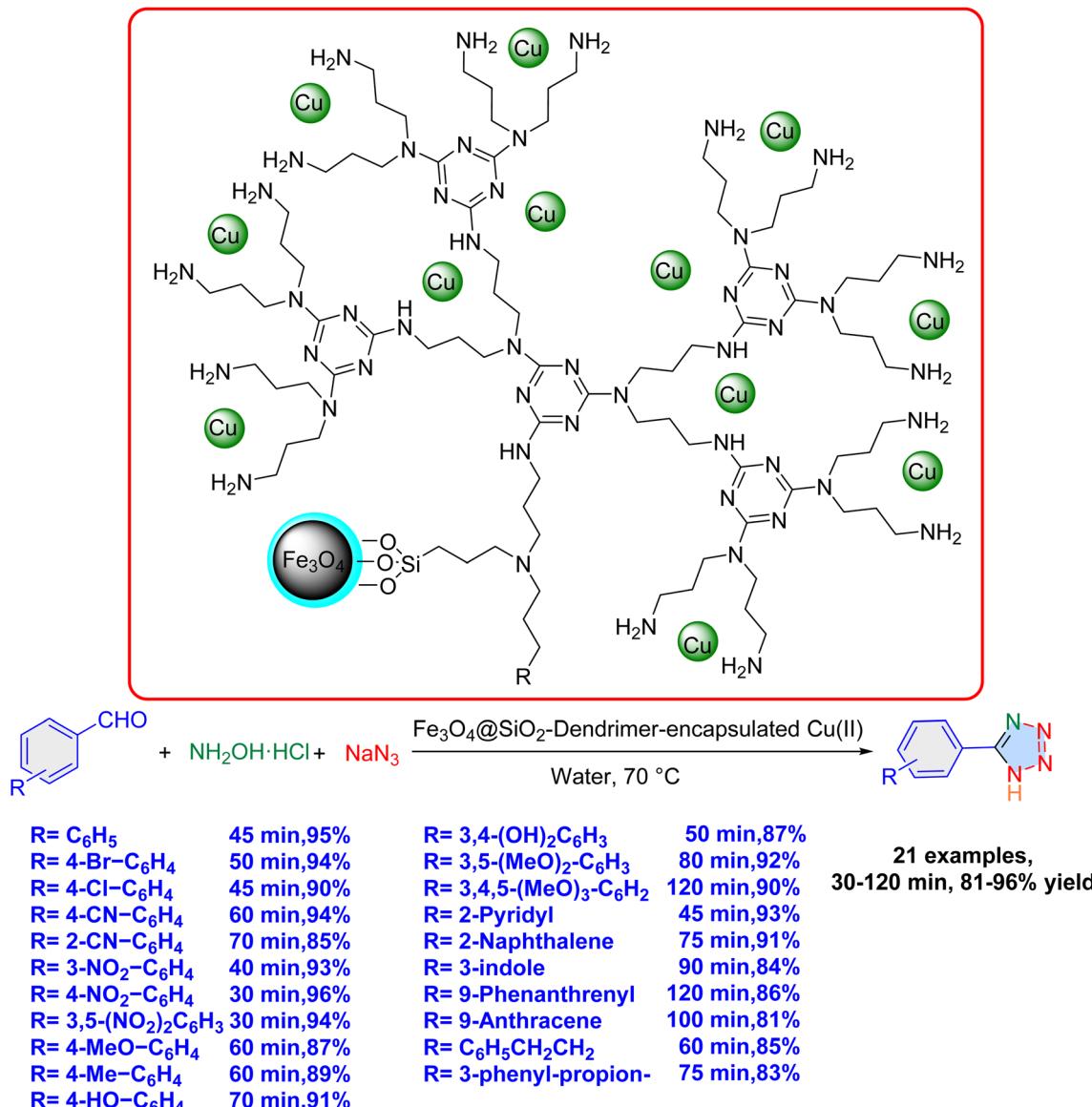


Scheme 15 CuNPs@N-GQDs@APTES catalyzed synthesis of 5-substituted tetrazoles.

performed in water emerging as the most efficient and green solvent, providing yields of 85–96% within 80–240 min. Substrate scope evaluation revealed that aldehydes bearing electron-withdrawing groups, such as nitro, enhanced yields due to increased carbonyl electrophilicity, while electron-donating substituents also gave high efficiencies. Steric hindrance from *ortho*-substituents modestly prolonged reaction times but did not significantly compromise yields. Mechanistically, the Lewis acid sites in catalyst activates aldehydes toward oxime formation, followed by Cu-mediated activation of the C=N bond, enabling [3 + 2] cycloaddition with azide to afford tetrazoles and the role of amine sites is the deprotonation of intermediates. This green, room-temperature protocol demonstrates superior efficiency compared to previous copper-

based methods requiring organic solvents or elevated temperatures. Overall, this study highlights the structural design and heterogeneous advantages of CuNPs@N-GQDs@APTES as a robust and recyclable nanocatalyst, contributing a sustainable route for high-yielding tetrazole synthesis with broad substrate applicability.

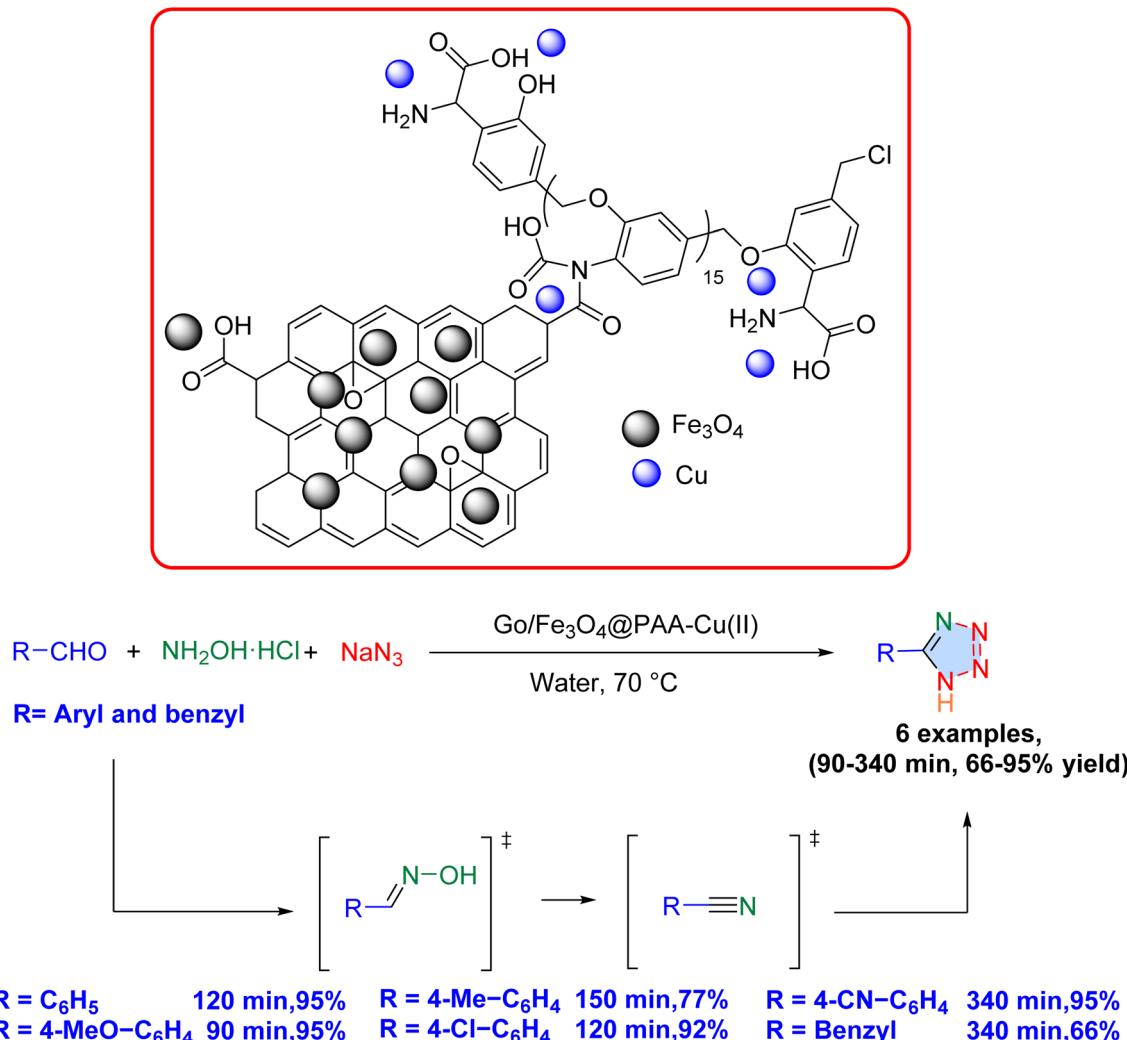
2.1.1.5. Cu/magnetic particles. Esmaeilpour and his team work in 2017 presented a dendrimer-encapsulated Cu(II) nanoparticle catalyst immobilized on superparamagnetic $\text{Fe}_3\text{O}_4@\text{SiO}_2$, designed for the green synthesis of 5-substituted 1*H*-tetrazoles *via* a one-pot, three-component synthesis of 5-substituted 1*H*-tetrazoles.⁵⁰ Characterization of the resulting nanocomposite revealed that it consists of 0.51 mmol g⁻¹ of copper within 50 nm spherical core-shell particles. The reaction



Scheme 16 $\text{Fe}_3\text{O}_4@\text{SiO}_2$ -dendrimer-encapsulated Cu(II) catalyzed the synthesis of 5-substituted 1H-tetrazoles from aldehyde synthons.

was shown to be dependent on the content during optimization, evidenced by decreased efficiency with lower amounts of the – containing catalyst and complete failure without it. The catalyst, displayed high activity under mild conditions, affording excellent yields (83–96%) within short reaction times (30–120 min) (Scheme 16). Notably, the aqueous medium served as a green solvent, eliminating the need for toxic or hazardous organic solvents, aligning with green chemistry principles. The study highlighted the influence of electronic and steric factors of aldehyde substituents on reactivity: electron-withdrawing groups enhanced reaction rates and yields, while electron-donating groups and sterically hindered substrates, such as 2-cyanobenzaldehyde and bulky polycyclic aldehydes, required longer times and gave slightly lower yields. Heteroaromatic aldehydes (e.g., pyridinecarboxaldehyde, indolecarboxaldehyde) also participated efficiently, demonstrating the broad substrate

scope. The magnetic and heterogeneous nature of the catalyst allowed facile separation *via* an external magnet and reusability for up to seven cycles without significant loss of activity or copper leaching. Authors suggested that the plausible mechanism involves initial oxime formation, Cu(II)-mediated activation of the C=N bond, and subsequent [3 + 2] cycloaddition with NaN_3 , releasing water and forming the tetrazole ring. This methodology offers several advantages: low catalyst loading, magnetic recoverability, mild aqueous conditions, minimal metal leaching, and broad functional group tolerance, making it a promising, sustainable approach for tetrazole synthesis. Its dendrimeric architecture provides high metal dispersion, enhancing catalytic efficiency and stability, while the core–shell $\text{Fe}_3\text{O}_4@\text{SiO}_2$ structure ensures biocompatibility and prevents nanoparticle aggregation.

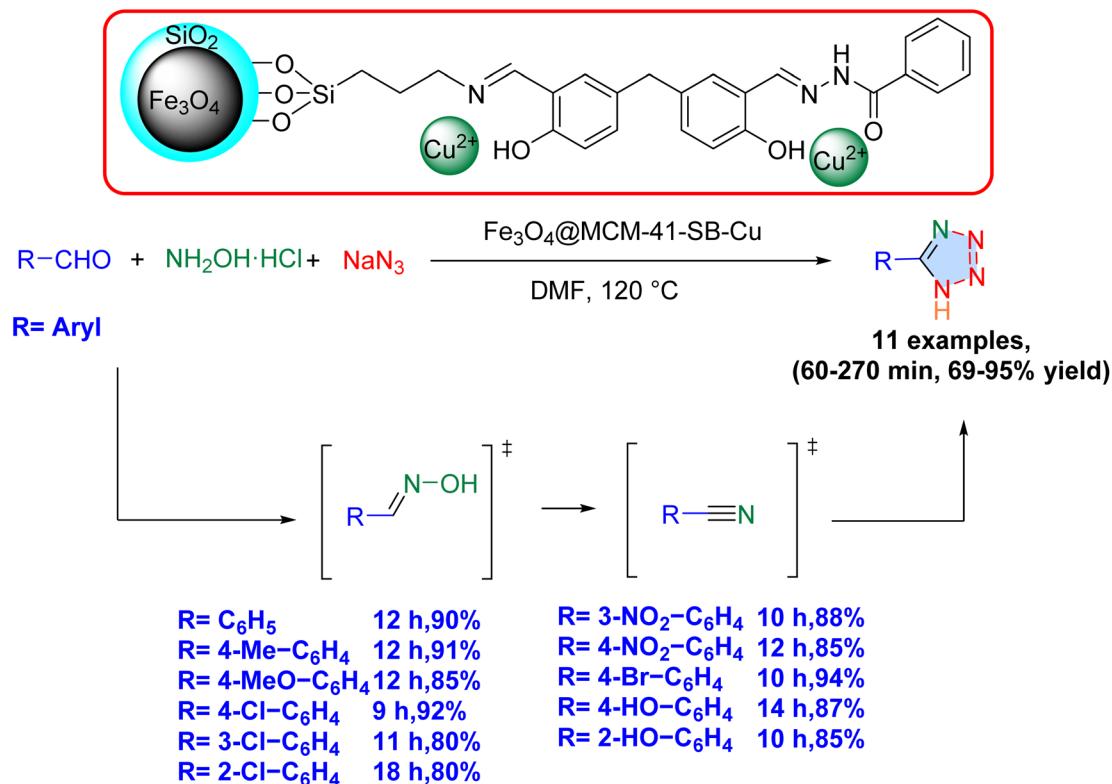


Scheme 17 GO/Fe₃O₄@PAA-Cu(II) catalyzed one-pot synthesis of 5-substituted 1*H*-tetrazoles in water.

Kazemnejadi and coworkers reported the development of a magnetically recoverable nanocatalyst, GO/Fe₃O₄@PAA-Cu(II), for the efficient synthesis of 5-substituted and 1-substituted tetrazoles *via* a one-pot, multicomponent approach.⁵¹ The catalyst consists of a poly(α -amino acid)-Cu(II) complex immobilized on magnetite graphene oxide, offering high thermal stability, large surface area, and facile separation through an external magnet. The copper (Cu) content in obtained catalyst was found to be 3.3 wt% (by EDX) or 0.52 mmol of Cu per 1 g (by ICP), the material has a near-spherical core-shell morphology with an average diameter of approximately 30 nm and exhibits superparamagnetic properties. The synthetic strategy demonstrates broad applicability toward aromatic and benzylic aldehydes, including electron-withdrawing and electron-donating substituents, with significant variations in reaction rate due to electronic effects. Electron-withdrawing groups facilitated slower conversion, but afforded higher yields (Scheme 17). The reactions proceeded in green solvents, with water proving optimal for aldehydes, PEG-400 for nitriles, and solvent-free conditions for amines as the synthons. The catalyst enabled

high to excellent yields (up to 98%) under mild conditions (70–100 °C), with recyclability over six cycles and negligible Cu leaching. A plausible mechanism involving Cu(II)-assisted activation of oximes or aldehydes followed by [3 + 2] azide cycloaddition was proposed. Interestingly, oximes provided a more facile route than nitriles, indicating distinct mechanistic pathways. The system aligns with sustainable chemistry principles by avoiding toxic solvents, utilizing low catalyst loading (1 mol%), and maintaining chemoselectivity even in mixed substrates. Overall, this study introduces a versatile, stable, and eco-friendly catalytic platform for tetrazole synthesis, with potential applicability in pharmaceuticals, materials science, and fine chemicals production.

The design and application of a Cu(II)-Schiff base complex anchored on magnetic mesoporous silica nanoparticles (Fe₃O₄@MCM-41-SB-Cu) as an efficient, reusable catalyst for the one-pot synthesis of 5-substituted-1*H*-tetrazoles was reported by Ahmadi and coworkers (Scheme 18).⁵² The catalyst was synthesized through stepwise functionalization of Fe₃O₄@MCM-41 with *N*-(2-aminoethyl)-3-aminopropyltrimethoxysilane, condensation with



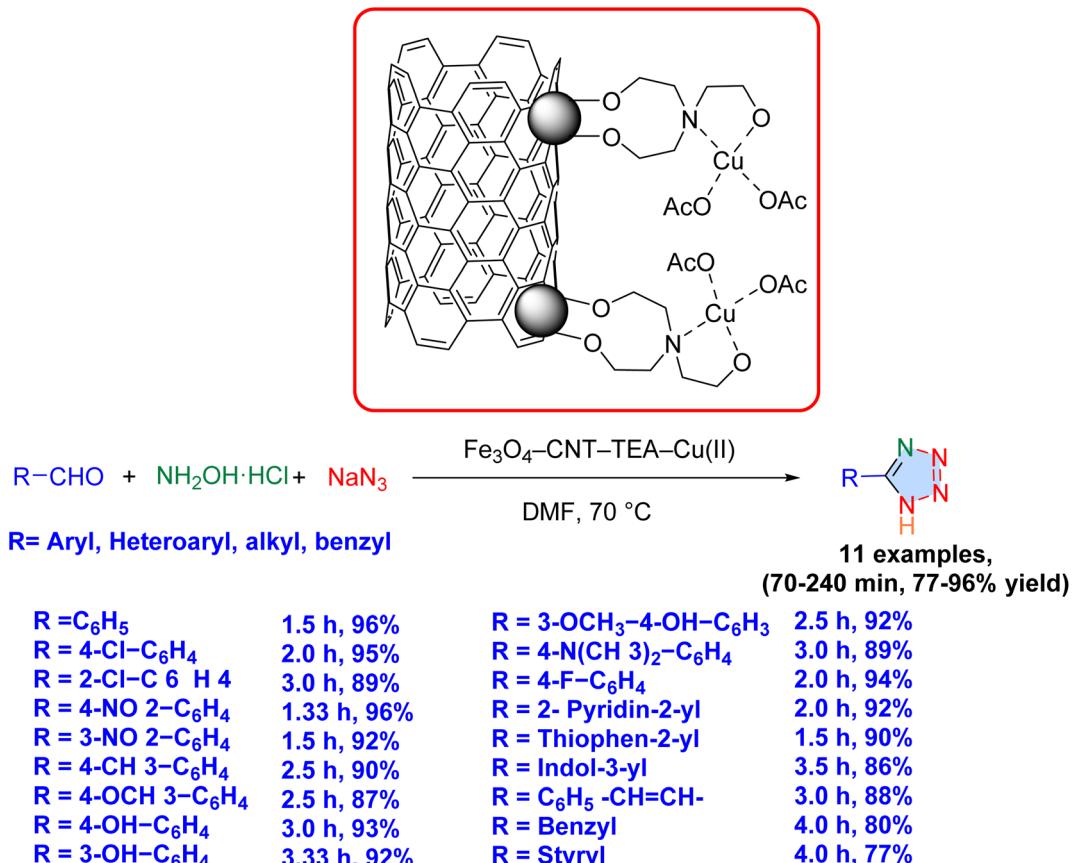
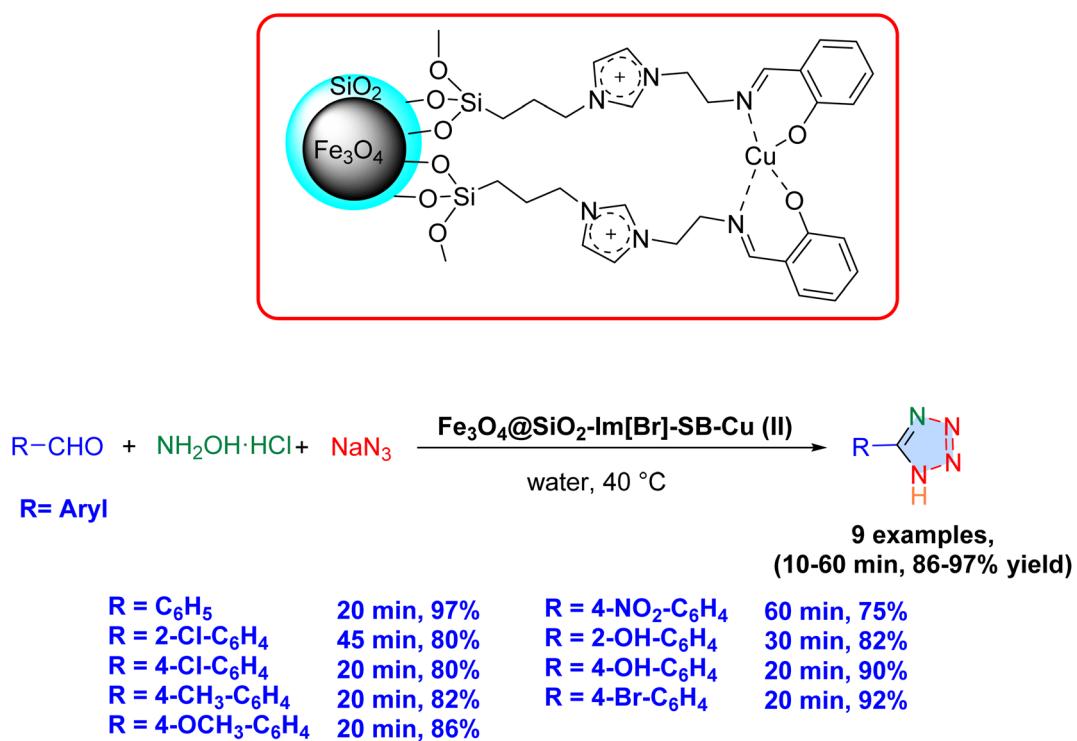
Scheme 18 GO/Fe₃O₄@PAA-Cu(II) catalyzed one-pot synthesis of 5-substituted 1H-tetrazoles in water.

5,5'-methylene bis(salicylaldehyde) and benzhydrazide, followed by coordination with Cu(OAc)₂·H₂O. The catalytic system promotes [3 + 2] cycloaddition of various aromatic aldehydes, hydroxylamine hydrochloride, and sodium azide in DMF at 120 °C using 30 mg catalyst, achieving excellent yields (69–95%) with broad substrate scope. Aldehydes bearing electron-withdrawing groups exhibited higher reactivity and shorter reaction times compared to electron-donating ones, demonstrating both electronic and steric influences on the reaction rate. The authors proposed that plausible mechanism involves the conversion of aldehyde to nitrile, and cycloaddition with azide to afford tetrazoles. The nanocatalyst demonstrated excellent recyclability, retaining >80% activity after five cycles with negligible copper leaching and straightforward magnetic separation. Additional investigations revealed its potential for α -amylase immobilization and enhanced antibacterial activity when loaded with streptomycin, particularly under magnetic field exposure. This work provides a robust, magnetically recoverable catalytic system with dual functionality in catalysis and biomedicine, offering greener reaction conditions, ease of separation, and high efficiency for the synthesis of pharmaceutically relevant tetrazole scaffolds.

In another interesting study Akbarzadeh *et al.* report a novel, magnetically recyclable heterogeneous catalyst, Fe₃O₄-CNT-TEA-Cu(II), for the synthesis of 5-substituted 1H-tetrazoles (Scheme 19).⁵³ The catalyst's structure is a magnetite-carbon nanotube (Fe₃O₄-CNT) composite that is functionalized with triethanolamine (TEA) to immobilize copper(II) nanoparticles. The prepared nanocomposite contains 3.37 wt% Cu (0.53 mmol

g⁻¹) and about 42 wt% Fe₃O₄, with Fe₃O₄ nanoparticles about 31 nm in diameter uniformly dispersed on CNTs. The TEA ligand donates O and N atoms that coordinate with Cu(II), enabling interactions with reagent functional groups and facilitating catalytic activation. The simple, one-pot, three-component reaction utilizes aromatic aldehydes, hydroxylamine, and sodium azide. The authors effectively demonstrate that the reaction conditions of 70 °C in DMF with low catalyst loading (0.005 g) facilitate the high-yield synthesis of tetrazoles. A notable strength of this work is the wide scope of substrates. The catalyst performs well with a variety of aliphatic, benzyl, aryl and heteroaryl aldehydes, regardless of the electronic and steric effects of the substituents, demonstrating its versatility. The authors propose a plausible mechanism in which the oxime directly reacts with the azide, which suggest that no nitrile intermediate is formed. From a practical perspective, the catalyst exhibits excellent reusability, a significant advantage for sustainable chemistry. It can be easily separated from the reaction mixture using an external magnet, minimizing catalyst loss and simplifying the workup.

In 2022, Mashhoori and Sandaroos reported a copper-based magnetic nanocatalyst, Fe₃O₄@SiO₂-Im[Br]-SB-Cu(II), as an efficient platform for the synthesis of 5-substituted 1H-tetrazoles under mild aqueous conditions (Scheme 20).⁵⁴ The catalyst was constructed through sequential fabrication steps: co-precipitation of Fe₃O₄ nanoparticles, silica coating, immobilization of imidazolium-based ionic liquid [Im][Br], subsequent Schiff-base functionalization, and final anchoring of Cu(II).

Scheme 19 $\text{Fe}_3\text{O}_4\text{-CNT-TEA-Cu(II)}$ catalyzed one-pot synthesis of 5-substituted 1H -tetrazoles.Scheme 20 Water-mediated synthesis of 5-substituted 1H -tetrazoles using $\text{Fe}_3\text{O}_4@\text{SiO}_2\text{-Im[Br]-SB-Cu(II)}$ nanocatalyst.

Spectroscopic, microscopic, and magnetic analyses confirmed its spherical and irregular shaped morphology with average particles size of 24 nm, and strong paramagnetic behavior with the Ms value of about 38 emu g⁻¹, which facilitated both structural robustness and convenient magnetic separation. ICP-OES analysis confirmed the copper loading on the nano-catalyst to be approximately 0.72 mmol g⁻¹. Catalytic studies revealed that only 0.9 mol% of the nanocatalyst (0.012 g) in water at 40 °C effectively promoted the three-component condensation of aldehydes, hydroxylamine hydrochloride, and sodium azide. The system provided excellent yields within short reaction times, highlighting the mildness and green character of the protocol. Electronic factors strongly influenced reactivity: aryl aldehydes bearing electron-withdrawing groups reacted more rapidly and in higher yields, while electron-donating substituents retarded conversion. Steric hindrance at *ortho* positions further reduced activity. Interestingly, the method was equally applicable to benzyl, aliphatic, and conjugated heteroaryl aldehydes, underscoring its broad substrate scope. Mechanistically, the reaction proceeds *via* oxime formation followed by direct azide attack, without involving nitrile intermediates. It is worth to mention that, investigation into the support material's role revealed modest activity, with yields of 30% for Fe₃O₄ and 50% for Fe₃O₄@SiO₂-Im[Br] after 24 h (compared to a baseline of 0% without a catalyst). However, stabilizing copper on the support led to a 97% yield in only 20 min. These results clearly establish the copper complex as the essential catalytic species. Furthermore, the substantial increase in rate suggests important synergistic effects, likely involving the oxygen and nitrogen atoms of the ligand interacting with reagent functional groups to promote the desired transformation. The catalyst exhibited high recyclability, maintaining activity for multiple runs with negligible Cu leaching, thus combining sustainability with performance. This study not only demonstrates the utility of ionic liquid-modified supports in stabilizing copper centers but also exemplifies an environmentally benign strategy for accessing tetrazole derivatives with pharmaceutical relevance.

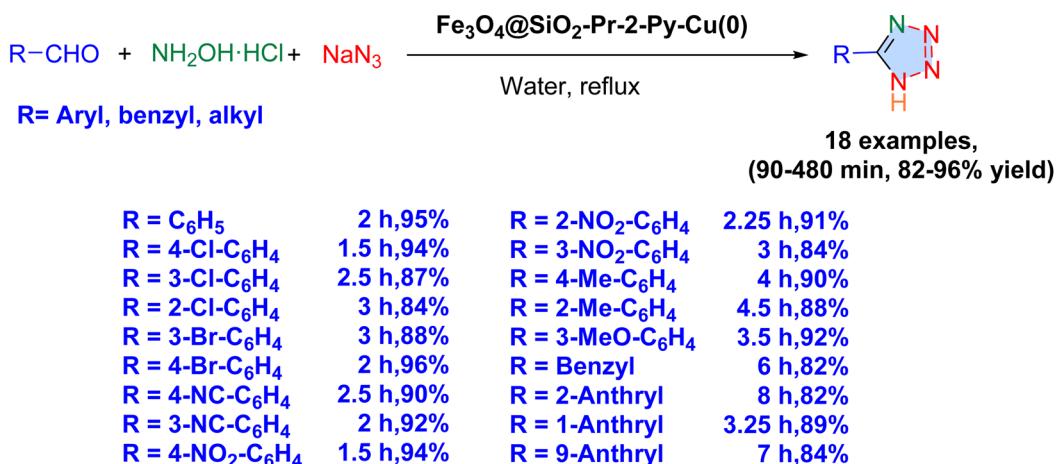
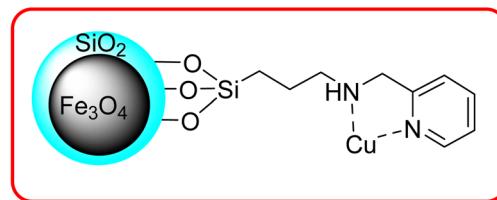
In 2025, Amiri and coworkers, introduces a copper(0)-based magnetically recoverable nanocatalyst, for the efficient synthesis of 5-substituted 1*H*-tetrazoles *via* this reaction (Scheme 21).⁵⁵ The catalyst was prepared through a multi-step strategy involving the synthesis and subsequent silica coating of Fe₃O₄, surface functionalization with grafting of 2-pyridyl imine containing silanol groups, the reduction of imine to amine using NaBH₄ and final immobilization of Cu(0) nanoparticles. The Fe₃O₄@SiO₂-Pr-2-Py-Cu(0) catalyst was characterized by a 0.25 mmol g⁻¹ copper content, a particle size of 31.1 nm, a specific BET surface area of 17.59 m² g⁻¹, and a total pore volume of 0.13 cm³ g⁻¹, with an average pore diameter of approximately 29.47 nm. The catalytic protocol (0.4 mol% catalyst in refluxing water) afforded tetrazoles in high yields (82–96%) under relatively mild and green conditions but increasing the amount further provided no additional improvement. Substrate scope investigations revealed distinct electronic and steric effects: aryl aldehydes with electron-withdrawing groups were more reactive due to enhanced electrophilicity at the carbonyl center, while electron-donating

groups gave slightly lower yields. Steric hindrance in *ortho*-substituted aryl aldehydes reduced reactivity. Benzyl aldehydes produced moderate yields, highlighting the broad applicability of the system. The authors suggested that the reaction proceeds *via* oxime formation followed by direct reaction with azide, rather than the classical nitrile pathway. This mechanistic insight underscores the unique role of the immobilized Cu(0) sites in facilitating C–N bond formation. The study is significant as it combines high efficiency, eco-friendly conditions, easy catalyst recovery, and a mechanistic departure from the nitrile route, making Fe₃O₄@SiO₂-Pr-2-Py-Cu(0) a promising nanocatalyst for sustainable tetrazole synthesis.

Eslahi *et al.* reported the design and application of another copper-based magnetic nanocatalyst, where Cu(II) ions are anchored onto glucosamine-functionalized Fe₃O₄@SiO₂, which exhibited excellent catalytic activity in the one-pot, three-component synthesis of 5-substituted 1*H*-tetrazoles (Scheme 22).⁵⁶ The catalyst was prepared through sequential coating of Fe₃O₄ with silica, functionalization with triazine and glucosamine, followed by immobilization of Cu(II). Characterizations confirmed the successful synthesis of Fe₃O₄@SiO₂-TCT-GA-Cu(II) MNPs, featuring a copper loading of 0.36 mmol g⁻¹, nanoscale particle sizes of approximately 25–30 nm, thermal stability, and superparamagnetic nature of the material, enabling facile recovery using an external magnet. Catalytic activity was optimized using benzaldehyde, sodium azide, and hydroxylamine hydrochloride. The best results were achieved in ethylene glycol/H₂O (1 : 1) at 90 °C using only 0.5 mol% Cu, affording tetrazoles in up to 97% yield within 1.5 h. Increasing the catalyst amount did not lead to a significant improvement in yield, while decreasing it slightly reduced the reaction efficiency. These results indicate that the reaction performance is dependent on the copper content, with 0.5 mol% Cu identified as the optimal loading. Substrate scope studies revealed that aryl aldehydes bearing electron-withdrawing substituents furnished tetrazoles rapidly in excellent yields, while electron-donating groups required longer times. *Ortho*-Substituted aryl aldehydes showed reduced reactivity due to steric hindrance. Aliphatic, benzyl, and heteroaromatic aldehydes were also well tolerated. The reaction plausibly proceeds *via* *in situ* oxime formation followed by a nitrile-mediated [3 + 2] cycloaddition with azide. Recyclability tests demonstrated that the catalyst retained activity for at least seven runs with negligible Cu leaching, highlighting its stability and green credentials. Compared to conventional homogeneous systems, this nanocatalyst operates under milder, greener conditions with higher turnover frequency, minimal metal loading, and straightforward recovery. Overall, the study presents a robust, eco-friendly approach to tetrazole synthesis with valuable insights into substituent electronic and steric effects on aldehyde reactivity.

Yadollahi and co-workers reported an efficient route to 5-substituted tetrazoles through a novel magnetic mixed-metal MOF catalyst, CoFe₂O₄/[Cu_{0.63}/Zn_{0.37}-TMU-17-NH₂] (Scheme 23).⁴² The catalyst was designed *via* a tandem procedure involving preparation of CoFe₂O₄ nanoparticles by co-precipitation, embedded during the solvothermal formation of Zn-TMU-17-NH₂, and subsequently subjected to post-





Scheme 21 $\text{Fe}_3\text{O}_4@\text{SiO}_2\text{-Pr-2-Py-Cu(0)}$ catalyzed the synthesis of 5-substituted 1*H*-tetrazoles.

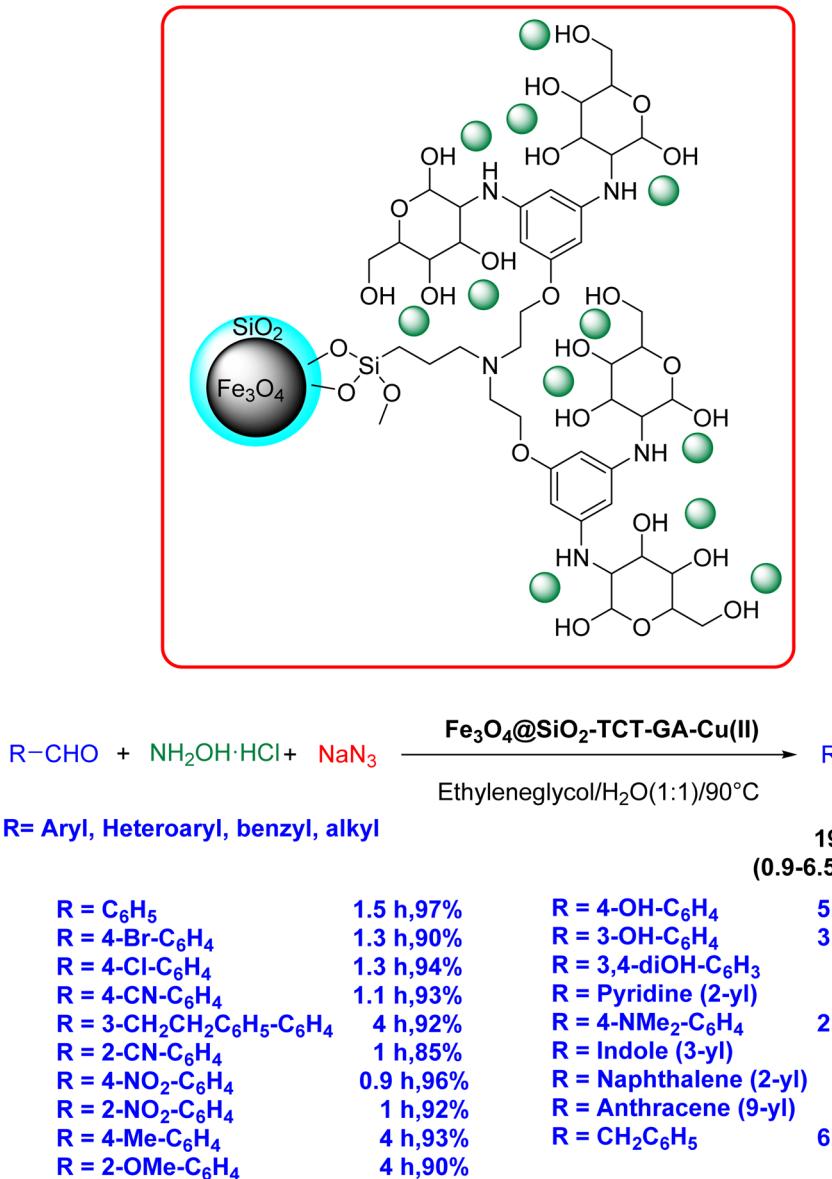
synthetic Cu(II) ion exchange. Structural analyses confirmed successful partial transmetalation while preserving framework integrity and semi-spherical morphology. Magnetic measurements demonstrated retained properties, enabling facile separation with an external magnet. Catalytic evaluation in the one-pot three-component condensation of aldehydes, hydroxylamine hydrochloride, and sodium azide in DMF at 120 °C revealed outstanding activity. Benzaldehyde afforded tetrazole in 98% yield within 8 min, far exceeding the performance of single-metal MOFs. The catalyst accommodated both electron-rich and electron-deficient aromatic aldehydes; the latter reacted more rapidly due to enhanced electrophilicity of the carbonyl group. Sterically hindered aldehydes showed slightly prolonged reaction times, while heteroaromatic substrates such as indole-3-carboxaldehyde also reacted efficiently. Di-aldehydes delivered bis-tetrazoles in excellent yields, confirming broad applicability. Mechanistically, the process involves aldehyde activation, oxime formation, and dehydration to a nitrile intermediate, which undergoes [3 + 2] cycloaddition with azide. The nanocomposite was readily recovered magnetically and reused for at least five cycles without significant loss of activity. Hot filtration and ICP analysis indicated negligible leaching of Cu or Zn, and PXRD confirmed structural stability. Collectively, this work illustrates how tandem magnetization and metal exchange yield a robust, recyclable, and green catalyst for rapid tetrazole synthesis.

2.1.2. Catalytic systems based on other metals

2.1.2.1. *Catalytic systems based on Ru.* In 2021 Vinoth *et al.* reported the application of a new series of half-sandwich (η^6 -*p*-

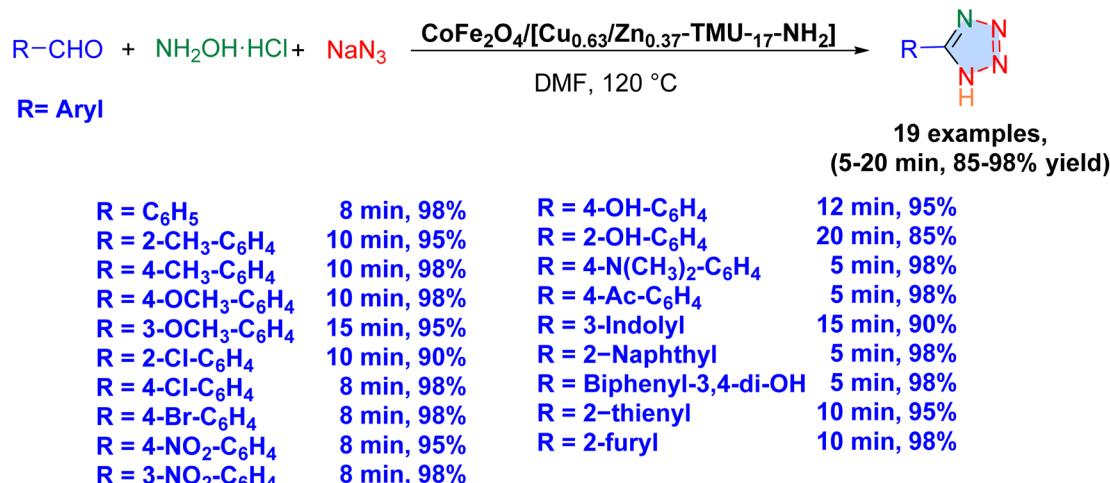
cymene) ruthenium(II) complexes bearing thiophene-2-carboxylic acid hydrazone ligands as efficient catalysts for multicomponent synthesis of tetrazoles (Scheme 24).³⁸ The catalytic complexes were synthesized through the reaction of $[\text{Ru}(\eta^6\text{-}p\text{-cymene})\text{Cl}_2]_2$ with hydrazone ligands derived from thiophene-2-carboxylic acid hydrazide and aromatic aldehydes, affording structurally well-defined piano-stool geometries confirmed by IR, UV-Vis, NMR, mass spectrometry, and single-crystal X-ray diffraction. The coordination of imidolate oxygen and azomethine nitrogen to Ru(II) played a pivotal role in catalytic stability and reactivity. The complexes were applied in one-pot, three-component syntheses of 5-substituted 1*H*-tetrazoles and the pyrene-based complex exhibited superior catalytic activity, attributed to enhanced π -conjugation effects stabilizing the transition states. In this transformation the aldehydes, hydroxylamine hydrochloride, and sodium azide were converted efficiently in DMF at 140 °C using only 0.5 mol% of catalyst and achieve excellent yields. Substrate scope evaluation demonstrated the versatility of the catalytic system, as the arylaldehydes, heteroarylaldehydes, conjugated aldehydes and aliphatic aldehydes all underwent smooth conversion. Both electron-donating and electron-withdrawing substituents exhibited negligible impact on yields, highlighting electronic tolerance, while steric hindrance from bulky groups produced only a modest reduction in efficiency. This methodological contribution underscores the potential of Ru(II) complexes as versatile catalysts for heterocyclic construction, offering broad substrate compatibility and efficient transformation pathways for tetrazole synthesis.



Scheme 22 $\text{Fe}_3\text{O}_4@\text{SiO}_2\text{-TCT-GA-Cu(II)}$ catalyzed one-pot synthesis of 5-substituted 1H -tetrazoles.

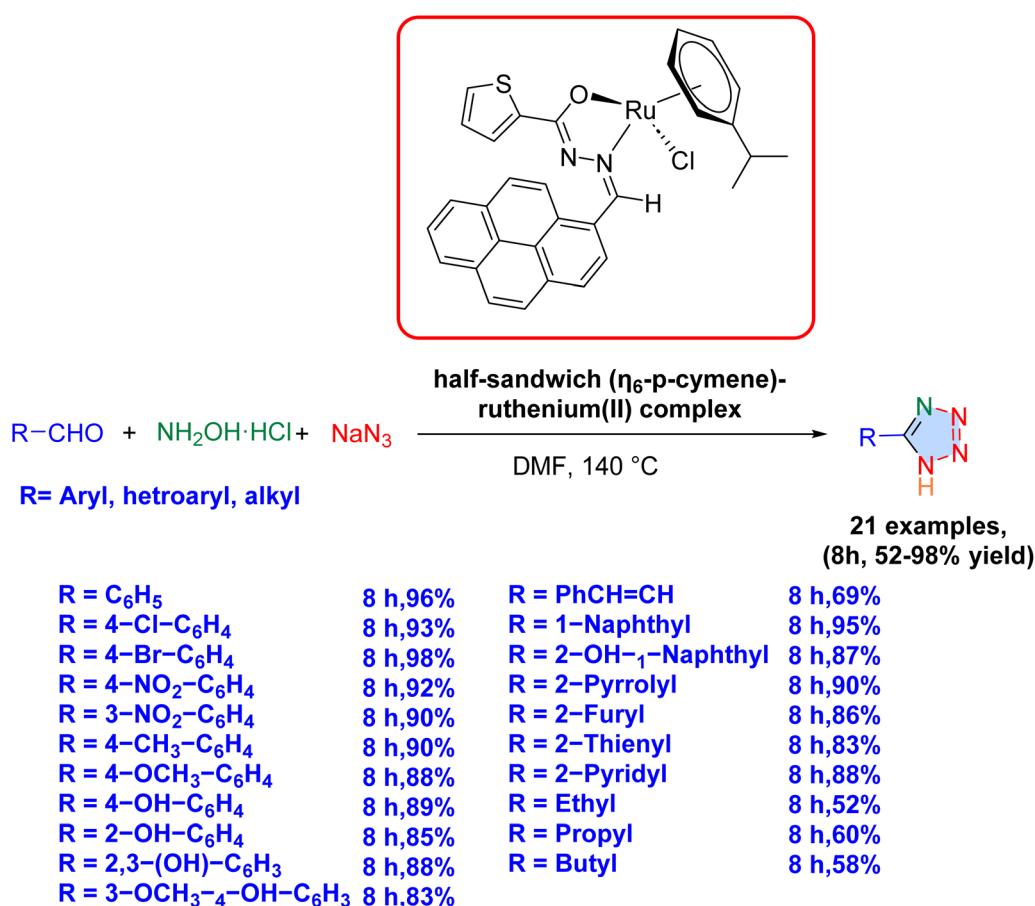
2.1.2.2. Catalytic systems based on Co. Mahmoudi *et al.* in 2021 reported a catalytic protocol for the synthesis of tetrazoles from aldehydes through an oxidation/multicomponent reaction domino strategy using a multifunctional redox catalyst (Scheme 25).³⁹ The system, based on a TEMPO/Co(III)-porphyrin/Ni(II) complex immobilized on magnetic nanoparticles derived from demetalated chlorophyll *b*, was shown to efficiently mediate both oxidation and reduction processes in a single catalytic framework. The characterizations shows that catalyst contains 2.04 W% Co and 1.07 W% Ni, yielding a Co/Ni atomic ratio of approximately 2 : 1, which is crucial for catalysis as the Co and Ni centers perform synergistic, distinct redox functions necessary for the overall domino reaction. From a mechanistic standpoint, the cobalt centers facilitated selective oxidation, nickel contributed to efficient nitro reduction, and TEMPO assisted radical processes, thereby achieving high

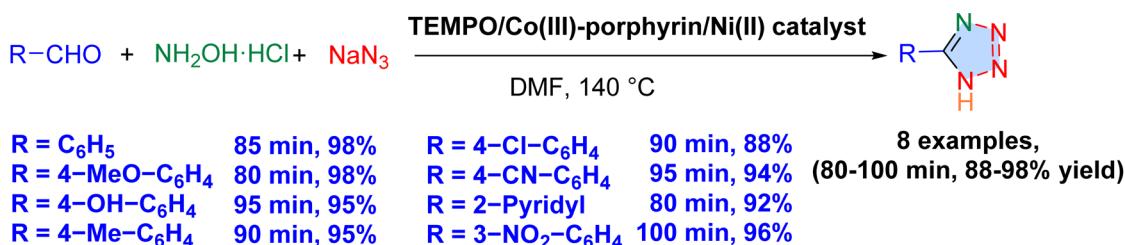
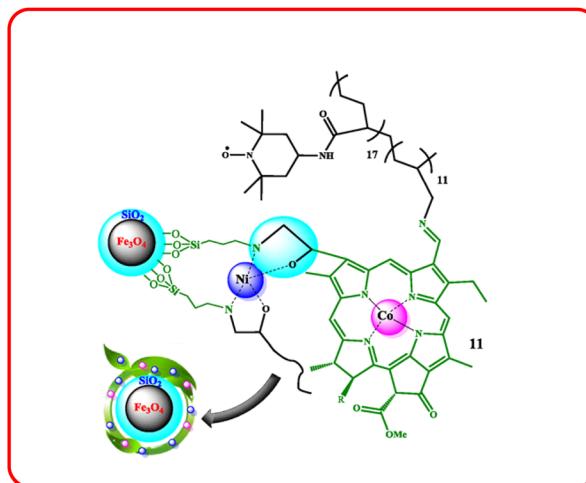
chemoselectivity and minimizing undesired by-products. In their study, aldehydes underwent conversion to 5-substituted 1H -tetrazoles within shorter reaction times (100–180 min) compared with nitriles (250–300 min), alkylbenzenes (180–220 min), and alcohols (120–180 min). This superior reactivity of aldehydes can be attributed to their inherent electrophilicity and their readiness to undergo nucleophilic attack by azide ions, which facilitates the subsequent [3 + 2] cycloaddition process. The authors also noted clear electronic and steric effects: aldehydes bearing electron-donating substituents such as $-\text{OMe}$ and $-\text{Me}$ showed slightly higher efficiencies and shorter reaction times, while those with electron-withdrawing groups like $-\text{Cl}$, $-\text{CN}$, or $-\text{NO}_2$ required longer reaction times but still afforded excellent yields, reflecting the stabilizing role of the catalyst in activating less reactive substrates. In contrast, alkylbenzenes required an initial oxidation step to form the

Scheme 23 CoFe₂O₄/[Cu_{0.63}/Zn_{0.37}-TMU-17-NH₂] catalyzed synthesis of 5-substituted tetrazoles.

aldehyde intermediate, resulting in longer reaction times and slightly reduced efficiencies, while nitriles also lagged behind due to their lower reactivity toward cycloaddition. Alcohols, although abundant and inexpensive, demanded preliminary oxidation to aldehydes, which extended the process. Overall, aldehydes emerged as the most direct and efficient precursors

for tetrazole formation in this system, with the electronic nature of substituents and steric hindrance around the carbonyl group playing decisive roles in modulating the reaction pathway and outcome. Reusability studies revealed that the catalyst could be recovered and reused for at least six consecutive cycles in the

Scheme 24 Half-sandwich (η⁶-p-cymene) ruthenium(II) complex catalyzed the synthesis of 5-substituted 1*H*-tetrazoles.



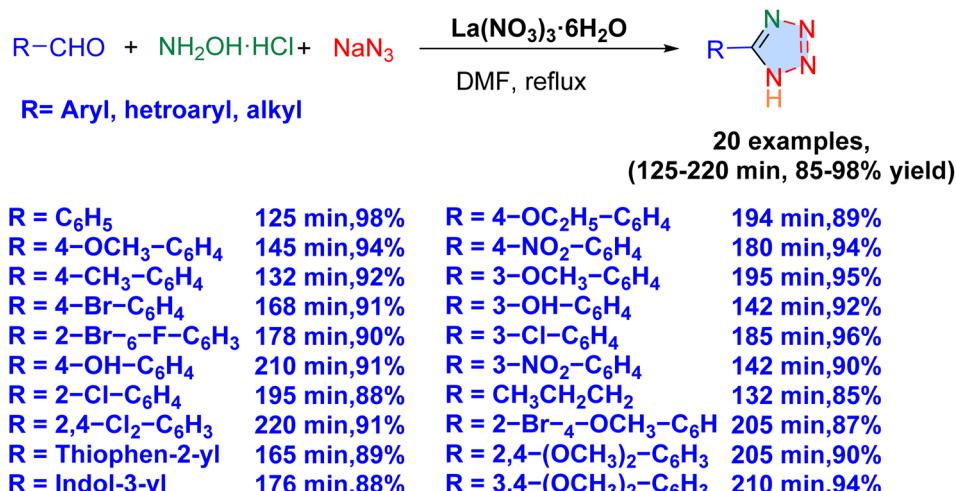
Scheme 25 $\text{Fe}_3\text{O}_4@\text{SiO}_2/\text{Ni}(\text{II})$ (TEMPO)-copolymer-(chlorophyll *b*)-Co(III) catalyzed the synthesis of 5-substituted 1*H*-tetrazoles.

synthesis of tetrazoles without significant loss of catalytic activity or selectivity, maintaining yields above 90%.

2.1.2.3. Catalytic systems based on lanthanides. In 2024 Gullapelli *et al.* introduces a sustainable catalytic protocol for the synthesis of 5-substituted 1*H*-tetrazoles directly from aldehydes using lanthanum(III) nitrate hexahydrate as a Lewis acid catalyst, highlighting its efficiency and broad substrate applicability (Scheme 26).³⁷ The procedure proceeds *via* a one-pot, three-component reaction involving aldehydes, hydroxylamine hydrochloride, and sodium azide in DMF under reflux, affording excellent yields (85–98%) with minimal by-products. Notably, the electronic nature and positional effects of substituents on the aldehyde ring markedly influenced reactivity and product yield. Aldehydes bearing electron-donating substituents, particularly at the *para* and *ortho* positions (*e.g.*, methoxy and methyl groups), facilitated superior yields due to enhanced stabilization of reaction intermediates, while those at *meta* positions displayed diminished reactivity. Conversely, electron-withdrawing groups exhibited variable effects: *meta*-substituted nitro and halogen derivatives provided comparatively higher yields than their *ortho* or *para* analogues, indicating that steric hindrance significantly modulates reactivity. The protocol also demonstrated compatibility with heteroaryl and aliphatic aldehydes, albeit with moderate to lower yields, underscoring the method's generality while revealing substrate sensitivity. Importantly, the catalytic system displayed excellent tolerance toward diverse functional groups without necessitating harsh

conditions or excess reagents, thus aligning with principles of green chemistry. The positive response across a wide range of aldehydes confirms lanthanum(III) nitrate hexahydrate as an effective, low-toxicity, and reusable catalyst for tetrazole synthesis, offering an environmentally benign and operationally simple alternative to conventional methods that often rely on corrosive, toxic, or less efficient systems.

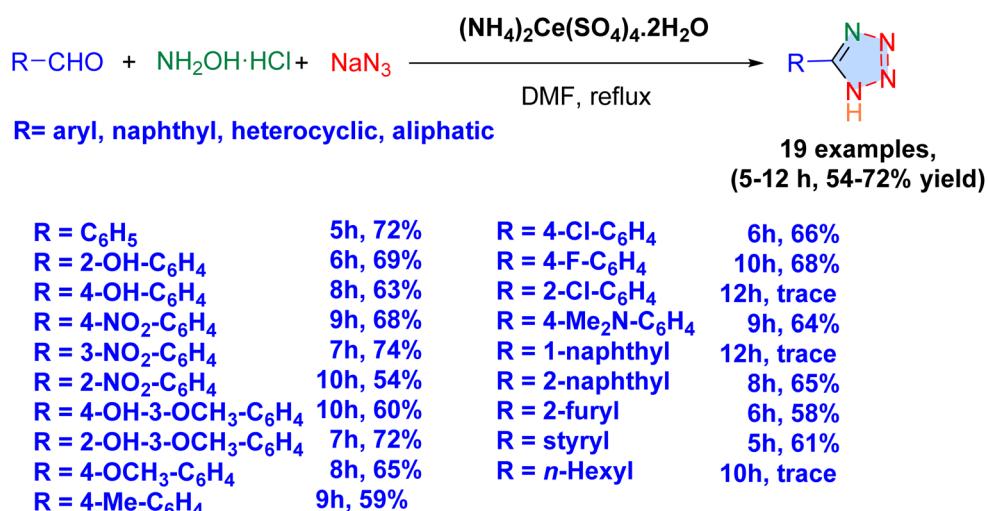
Mitra *et al.* introduces ceric ammonium sulphate (CAS) as a low-cost, non-toxic reusable catalyst for the three-component synthesis of 5-substituted 1*H*-tetrazoles (Scheme 27).⁵⁷ The reaction employs aldehydes, hydroxylamine hydrochloride, and sodium azide in refluxing DMF with 20 mol% catalyst, affording moderate to good yields (58–74%) within 5–12 h. The protocol is general for aromatic, heteroaromatic, aliphatic, and conjugated aldehydes. Electron-withdrawing substituents (*e.g.*, nitro, halogen) enhanced reactivity and yields, while electron-donating groups or sterically hindered substrates (*e.g.*, 2-nitro, 2-chloro, 1-naphthyl aldehydes) resulted in lower conversions or traces of product, underlining both steric and electronic effects on efficiency. Substitution patterns also influenced outcomes; *ortho*-hydroxy and *ortho*-methoxybenzaldehydes outperformed their *para*-analogues due to intramolecular hydrogen bonding that increased electrophilicity. Importantly, the suggested mechanism highlighting nitrile generation as the key step. A further point of interest lies in the catalyst's recyclability. Although unsupported, CAS was readily separated by filtration and reused up to five cycles with only gradual yield attenuation,

Scheme 26 La(NO₃)₃·6H₂O catalyzed synthesis of 5-substituted tetrazoles.

offering practical advantages for sustainable synthesis. The protocol avoids toxic nitriles, harsh conditions, or metal contamination, thus offering a green, cost-effective alternative for tetrazole synthesis with broad substrate tolerance.

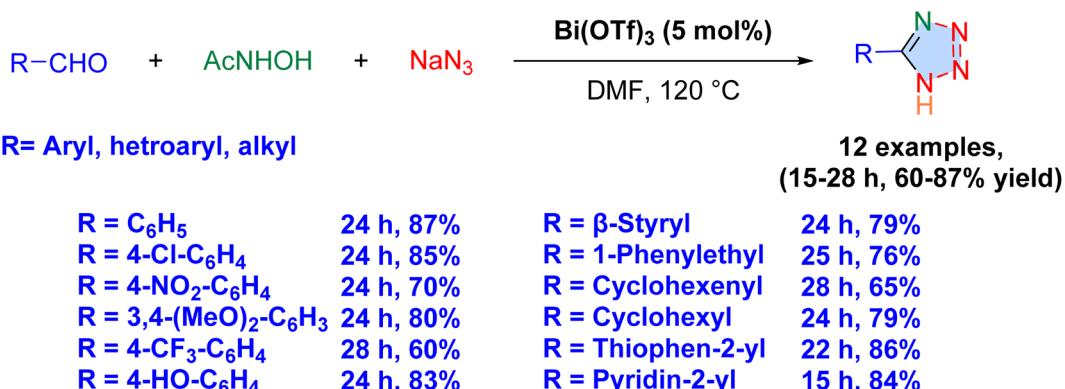
2.1.2.4. Catalytic systems based on heavy metals. Sridhar *et al.* (2013) introduced an innovative one-step method for synthesizing 5-substituted 1*H*-tetrazoles directly from aldehydes using acetohydroxamic acid (AHA) and sodium azide under Bi(OTf)₃ catalysis (Scheme 28).⁵⁸ Conducted in DMF at 120 °C with 5 mol% catalyst, the reaction provided tetrazoles in good to excellent yields (60–87%) over 15–28 h. The choice of solvent was critical: while acetonitrile stalled at the nitrile intermediate, DMF enabled efficient cycloaddition and exclusive tetrazole formation. The protocol proved effective across a wide range of aldehydes, including aromatic, heteroaromatic, aliphatic, and conjugated substrates. Aromatic aldehydes with electron-withdrawing substituents such as chloro and nitro provided consistently high yields (85% and 70%, respectively),

while trifluoromethyl-substituted aldehydes afforded somewhat lower efficiency (60%). Electron-donating substituents, exemplified by methoxy groups, also performed well, giving products in 80–83% yields. Conjugated aldehydes such as cinnamaldehyde and styryl derivatives reacted efficiently, affording tetrazoles in 79–83% yields, whereas more sterically hindered alicyclic substrates, such as norbornene and cyclohexenyl aldehydes, gave moderate yields (65–79%) under prolonged conditions. Importantly, heteroaromatic aldehydes such as thiophene and pyridine derivatives furnished excellent yields (86% and 84%, respectively), underscoring the broad substrate scope and functional group tolerance of this method. The use of AHA as a reagent is particularly distinctive, as it facilitates oxime and nitrile generation *in situ* before tetrazole formation. Beyond being a therapeutic agent (Lithostat®) and a chelating agent in nuclear processing, this work highlights its underexplored potential in synthetic heterocyclic chemistry. Combined with the mild, low-toxicity bismuth(III) catalyst, this strategy



Scheme 27 CAS catalyzed synthesis of 5-substituted tetrazoles.

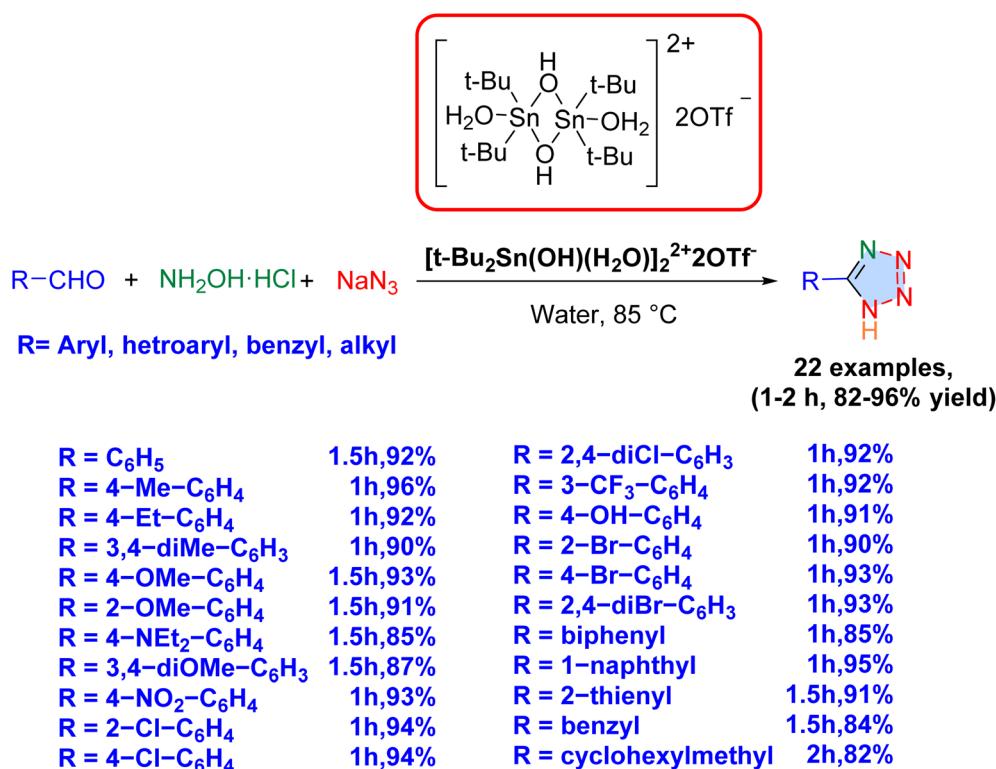


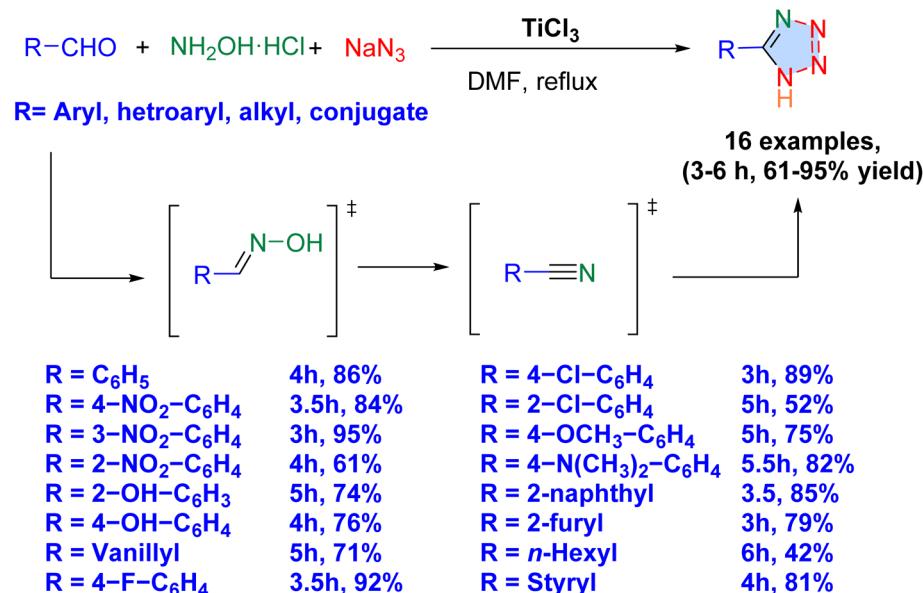
Scheme 28 Bi(OTf)₃ catalyzed synthesis of 5-substituted tetrazoles from aldehydes, acetohydroxamic acid and sodium azide.

offers a straightforward and environmentally considerate route to tetrazoles.

Wang *et al.* (2019) reported a one-pot, three-component synthesis of 5-substituted 1*H*-tetrazoles catalyzed by the air-stable cationic organotin cluster $[t\text{-Bu}_2\text{Sn}(\text{OH})(\text{H}_2\text{O})]_2^{2+}\cdot 2\text{OTf}^-$ (Scheme 29).⁴⁰ This dimeric cluster, characterized by hydroxyl bridges and six-coordinated tin centers, functions as a neutral Lewis acid, enabling efficient activation of substrates. Optimization studies established water as the superior medium, providing a 96% yield for 5-phenyl-1*H*-tetrazole at 85 °C with only 1 mol% catalyst in 1 h. Other solvents such as DMF, PEG-400, and DMSO resulted in diminished yields, while toluene and solvent-free conditions failed. The low catalyst loading and

the use of water as a green solvent underscore the sustainability of this method. The substrate scope included aromatic, aliphatic, heteroaromatic, and conjugated aldehydes, all affording good to excellent yields. Substituted aromatics bearing either electron-donating or electron-withdrawing groups reacted smoothly, showing minimal sensitivity to electronic effects. Steric hindrance, however, was more pronounced: *ortho*-substituted aromatics and bulky aliphatic aldehydes required longer times or gave slightly reduced yields compared to *para*- and *meta*-substituted analogues. Importantly, heterocyclic aldehydes such as thiophene and pyridine also participated efficiently, highlighting the broad compatibility of the system. Overall, this study demonstrates that the

Scheme 29 $[t\text{-Bu}_2\text{Sn}(\text{OH})(\text{H}_2\text{O})]_2^{2+}\cdot 2\text{OTf}^-$ catalyzed synthesis of 5-substituted tetrazoles.

Scheme 30 $TiCl_3$ -catalyzed synthesis of 5-substituted tetrazoles.

organotin cluster catalyst, combined with water as the reaction medium, offers a practical, eco-friendly, and highly effective route to tetrazole synthesis.

2.1.2.5. Catalytic systems based on *Ti*. Chakraborty and Ghosh (2018) developed a titanium trichloride ($TiCl_3$)-catalyzed one-pot multi component synthesis of 5-substituted $1H$ -tetrazoles from aldehydes, hydroxylamine hydrochloride, and sodium azide (Scheme 30).³⁶ The optimized conditions involved refluxing in DMF with 20 mol% $TiCl_3$, affording products in moderate to excellent yields (42–95%) within 3.5–6 h. The catalytic efficiency was strongly solvent- and temperature-dependent, with DMF under reflux giving the best results. Mechanistically proceeds *via* the *in situ* formation of nitrile as the key intermediates in this reaction as the control experiments confirmed that in the absence of $TiCl_3$ only nitriles were isolated, underscoring its crucial role in promoting the subsequent cycloaddition step for synthesis of 5-substituted $1H$ -tetrazoles. The scope of the reaction encompassed aliphatic, aromatic, and heterocyclic aldehydes, demonstrating broad applicability. Substituent effects were clearly observed: aldehydes bearing electron-withdrawing groups yielded products in higher efficiency and shorter times, due to increased electrophilicity of the nitrile intermediate. In contrast, electron-donating substituents and sterically hindered aldehydes led to lower conversions and longer reaction times. This methodology is notable for its use of an abundant, water-soluble, and relatively low-toxicity catalyst, straightforward work-up, and compatibility with diverse substrates. Compared to traditional multistep or heterogeneous catalytic systems, the $TiCl_3$ protocol offers a practical and environmentally considerate alternative for the efficient synthesis of bioactive tetrazole derivatives.

2.2. Catalytic systems based on nonmetals

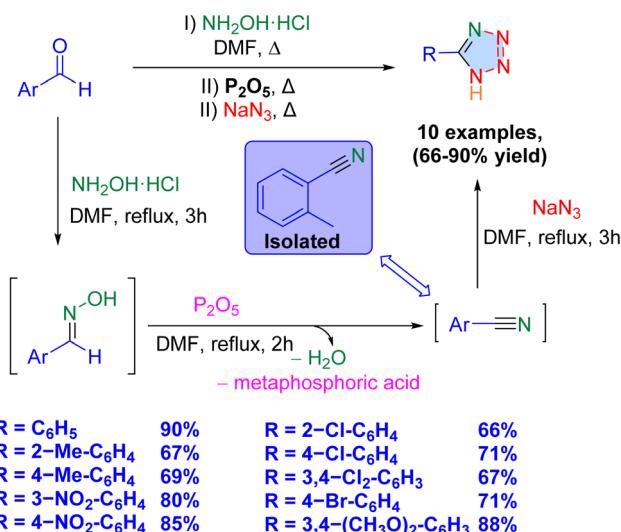
In a significant advancement for synthetic chemistry, Khan *et al.* developed an efficient one-pot protocol for converting

substituted benzaldehydes into 5-substituted- $1H$ -tetrazoles (Scheme 31).²⁴ This method is particularly notable because it avoids the need to isolate intermediate oximes and nitriles, streamlining the overall process. The reaction initiates with the formation of an oxime from a benzaldehyde and hydroxylamine hydrochloride in refluxing DMF, followed by *in situ* conversion to a nitrile facilitated by addition of a catalytic amount of phosphorus pentoxide (P_2O_5) dehydrating agent, to the reaction after 2 h. The nitrile then undergoes a [3 + 2] cycloaddition with an azide source, yielding the final tetrazole products in moderate to good yields after 3 h. The reaction generates *meta*-phosphoric acid as a byproduct, which is easily removed by washing. This approach offers a safer alternative to older methods that generated potentially explosive byproducts from ammonia and iodine. The comparison of the obtained yields shows that the electronic nature of the substituent on the benzaldehyde ring significantly influences their reactivity in production of tetrazole product. Electron-withdrawing groups (EWGs), such as nitro and halogens like chloro and bromo, generally result in higher yields, with a strong trend observed where the *para*-nitro group yields the highest at 90%. Conversely, electron-donating groups (EDGs), including, lead to lower yields, with the methyl group at the *para* position giving the lowest yield of 66%. This suggests that the reaction is favored by the presence of electron-withdrawing substituents. Furthermore, the position of the substituent also plays a role, as *para*-substituted compounds consistently show slightly higher yields than their *ortho*-substituted counterparts, likely due to a reduction in steric hindrance.

2.3. Reaction in acidic and basic media

Brønsted acid catalysis has long been a cornerstone of organic transformations, offering a simple yet powerful means of activating carbonyl compounds and promoting cascade processes. Within this context, Singh and Ahmed (2024) reported an



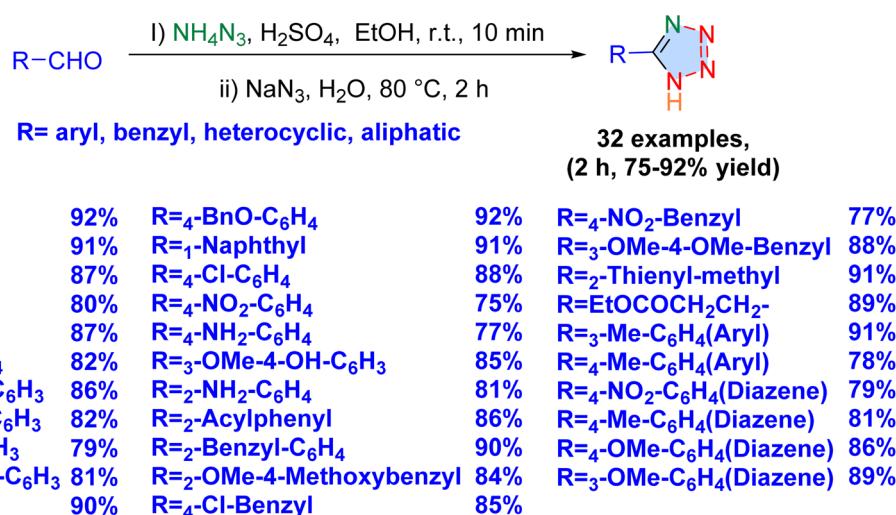


Scheme 31 One-pot synthesis of 5-substituted tetrazoles from their respective aldehydes over the catalysis of P_2O_5 .

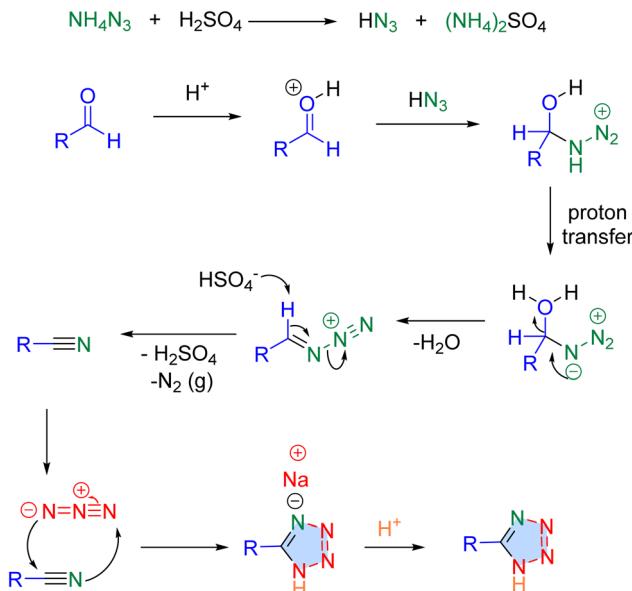
elegant H_2SO_4 -mediated one-pot synthesis of $1H$ -tetrazoles and 1-methyltetrazoles directly from aldehydes, employing ammonium or methyl azide as the nitrogen source (Scheme 32).⁵⁹ Unlike earlier approaches requiring metal catalysts, nanoparticles, or harsh conditions, this methodology proceeds under mild, metal-free conditions with ethanol and water as green solvents. The reaction is initiated by the *in situ* generation of hydrazoic acid from ammonium azide in the presence of sulfuric acid, which subsequently reacts with protonated aldehydes to furnish nitrile intermediates. These electrophilic species undergo [3 + 2] cycloaddition with sodium or methyl azide to yield tetrazoles, highlighting nitrile formation as the mechanistic pivot (Scheme 33). Optimization established EtOH at room temperature for the initial step and aqueous NaN_3 at 80 °C for the second, affording excellent yields (75–92%) within

2–2.5 h. The substrate scope encompasses aromatic, aliphatic, conjugated, and heteroaromatic aldehydes. Electron-withdrawing substituents generally enhanced efficiency, delivering tetrazoles in 87–91% yield, whereas electron-donating groups produced slightly reduced but still satisfactory yields (77–85%). Steric effects were evident, with *ortho*-substituted aldehydes sometimes giving lower conversions due to hindered approach of azide. Importantly, phenylacetaldehydes and disubstituted benzaldehydes were also tolerated, broadening the applicability of this method. Reaction times were consistently short (≤ 2.5 h), in sharp contrast to prior protocols requiring prolonged heating in high-boiling solvents such as DMF or DMSO. Other noteworthy aspects include scalability, demonstrated on gram scale with $\sim 80\%$ isolated yield, and the versatility of the protocol in accessing 1-methyltetrazoles by employing methyl azide. The operational simplicity, metal-free nature, and avoidance of toxic nitrile precursors make this approach a sustainable and practical alternative to conventional tetrazole syntheses. Nevertheless, safety considerations regarding azide handling remain essential, as the procedure relies on *in situ* generation of hydrazoic acid. Overall, this sulfuric acid-catalyzed cascade exemplifies how classical Brønsted acid activation can be combined with modern green chemistry principles to deliver efficient, high-yielding access to pharmacologically relevant tetrazoles.

In a similar procedure, humic acid was utilized as a novel, eco-friendly, and reusable catalyst for the one-pot, three-component synthesis of 5-substituted $1H$ -tetrazoles from aldehydes, hydroxylamine hydrochloride, and sodium azide in water (Scheme 34).⁶⁰ Humic acid, a high molecular weight natural polymer rich in carboxyl and phenolic groups, provides Brønsted acidity and micelle-like structures in aqueous media, which synergistically enhance catalytic efficiency. Optimization studies revealed water as the most effective solvent, affording up to 92% yield for benzaldehyde-derived products at 100 °C in 4 h, outperforming traditional solvents such as DMF or DMSO. The



Scheme 32 Sulfuric acid catalyzed synthesis of $1H$ -tetrazole and 1-methyltetrazoles from aldehydes, ammonium azide or methyl azide, and sodium azide.



Scheme 33 The plausible mechanism for sulfuric acid catalyzed synthesis of $1H$ -tetrazole and 1 -methyltetrazoles from aldehydes, ammonium azide and sodium azide.

method demonstrated broad substrate tolerance: aromatic aldehydes with both electron-donating and electron-withdrawing substituents produced tetrazoles in excellent yields, with minimal influence of steric or electronic effects; heteroaromatic and aliphatic aldehydes were equally well tolerated. Reaction times were generally short, and yields consistently high (often 85–92%). The mechanism involves humic acid – mediated activation of the aldehyde carbonyl, oxime formation, followed by [3 + 2] cycloaddition of azide and subsequent dehydration to give the tetrazole. A key advantage is the reusability of humic acid, which retained activity over five catalytic cycles. Compared to metal-based or halogen catalysts, this system is inexpensive, non-toxic, and sustainable, providing a green alternative for tetrazole synthesis with potential for scale-up.

In 2025 Ghasemzadeh *et al.* developed a multifunctional nanocomposite acid-catalyst, $\text{NiFe}_2\text{O}_4@\text{CA}@{\text{MIL}-53(\text{Fe})}@{\text{CQDs}-\text{SO}_3\text{H}}$, which integrates magnetic NiFe_2O_4 , porous $\text{MIL}-53(\text{Fe})$, carbon quantum dots, and sulfonic acid groups to provide synergistic Brønsted–Lewis acidity (Scheme 35).⁶¹ Structural characterization confirmed its stability, mesoporosity, and recyclability. The catalyst enabled the synthesis of 5-substituted tetrazoles and 4-aryl-1,2,3-triazoles from sodium azide, hydroxylamine hydrochloride (or nitromethane), and various aldehydes under DMF at $110\text{ }^\circ\text{C}$. Aromatic aldehydes bearing both electron-withdrawing and electron-donating substituents reacted efficiently, giving yields of 82–98% within 40–120 min. Electron-withdrawing groups generally accelerated reactions and improved yields, while *ortho*-substituents caused steric delays but still afforded high conversions. The proposed mechanism involves activation of aldehyde carbonyls by Lewis acidic Fe and Ni centers, followed by oxime formation and Brønsted acid – assisted [3 + 2] cycloaddition with azide. In

nitromethane-based reactions, nitroolefin intermediates undergo azide addition and cyclization to triazoles. Importantly, the catalyst is magnetically recoverable and reusable for at least five cycles without significant loss of activity. Compared to conventional systems, this protocol offers superior reaction times, higher atom economy, and environmentally benign conditions. The antibacterial screening of selected products further highlights the biomedical relevance of this approach.

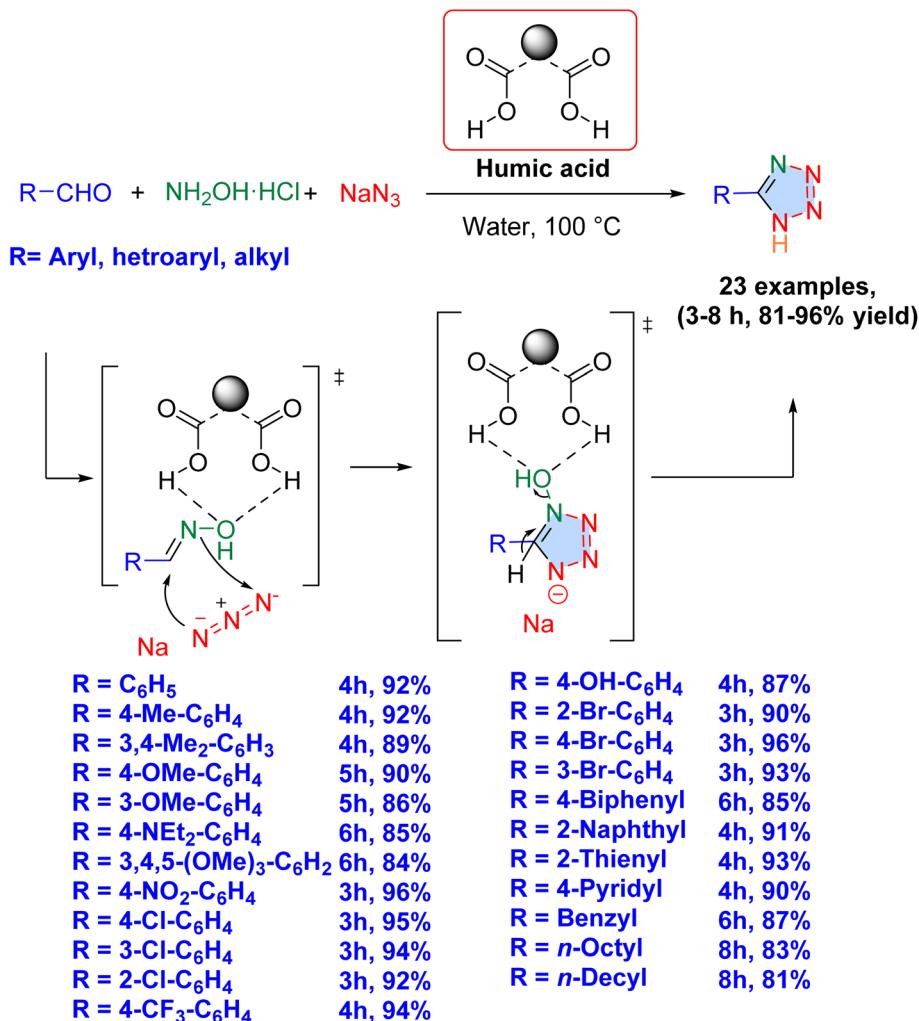
Iodine has long been recognized as a versatile, inexpensive, and environmentally benign reagent in organic synthesis, serving as both a mild oxidant and catalyst for diverse heterocyclic transformations.⁶³ Two noteworthy methodologies highlight its utility in the direct conversion of aldehydes to tetrazoles. Shie and Fang (2003) reported a one-pot tandem protocol in aqueous media combined with 1 mL of THF, where aldehydes were first converted into nitriles by iodine in ammonia water, followed by trapping with sodium azide in the presence of ZnBr_2 to yield 5-substituted tetrazoles in 72–89% yields at 12–48 h (Scheme 36, path a).²⁸ This approach accommodated aromatic, heteroaromatic, and aliphatic aldehydes, with electron-withdrawing substituents enhancing reactivity. The process proceeds *via* an *N*-iodo aldimine intermediate and exploits water as a green solvent, minimizing safety concerns associated with azide chemistry.

Building upon this foundation, Reddy and Pasha (2011) developed an iodine-catalyzed, one-pot protocol that bypassed isolation of nitrile intermediates. Conducted at $100\text{ }^\circ\text{C}$ with molecular iodine as the sole catalyst, the method offered shorter reaction times and comparable yields (65–90%) across a wide range of aryl aldehydes (Scheme 36, path b).²⁹ Both electron-donating and electron-withdrawing substituents were tolerated, with steric and electronic factors influencing efficiency modestly. The avoidance of metal promoters such as ZnBr_2 , combined with low catalyst loading and simplified workup, further enhanced the environmental and operational attractiveness of this method.

Mechanistically, both strategies rely on *in situ* nitrile formation, a transformation proceeding through the formation of an *N*-iodo aldimine intermediate followed by elimination of HI, and subsequent azide [3 + 2] cycloaddition to furnish tetrazoles. Together, these works demonstrate the evolution of iodine-mediated aldehyde-to-tetrazole transformations from aqueous, promoter-assisted systems toward metal-free and solvent-free conditions. Their collective contribution underscores iodine's versatility as a benign, inexpensive, and effective catalyst, making these protocols highly relevant for sustainable tetrazole synthesis.

In 2019, Nasseri *et al.* introduced an innovative catalyst-free and operationally simple method for one-pot synthesis of 5-substituted $1H$ -tetrazoles using a dimethyl sulfoxide–nitric acid ($\text{DMSO}-\text{HNO}_3$) system (Scheme 37).⁶⁴ The method proceeds from readily available aldehydes, hydroxylamine hydrochloride, and sodium azide under mild conditions ($40\text{ }^\circ\text{C}$), avoiding the need for preformed nitriles or transition-metal catalysts typically required in conventional approaches. This represents a valuable departure from the classical Hantzsch–Vagt protocol, which often suffers from high temperatures, toxic solvents, and



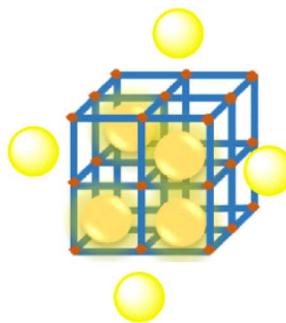
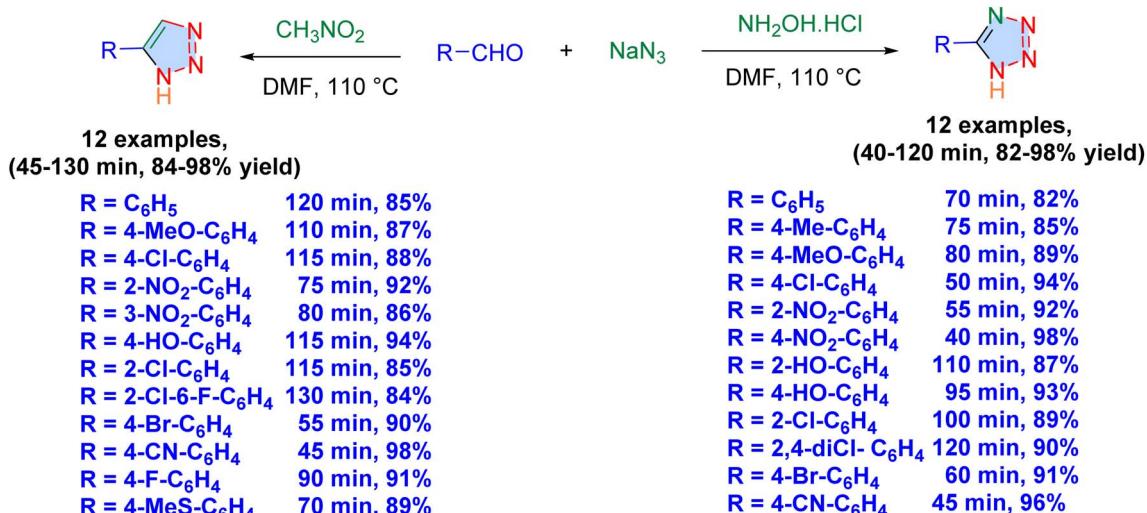
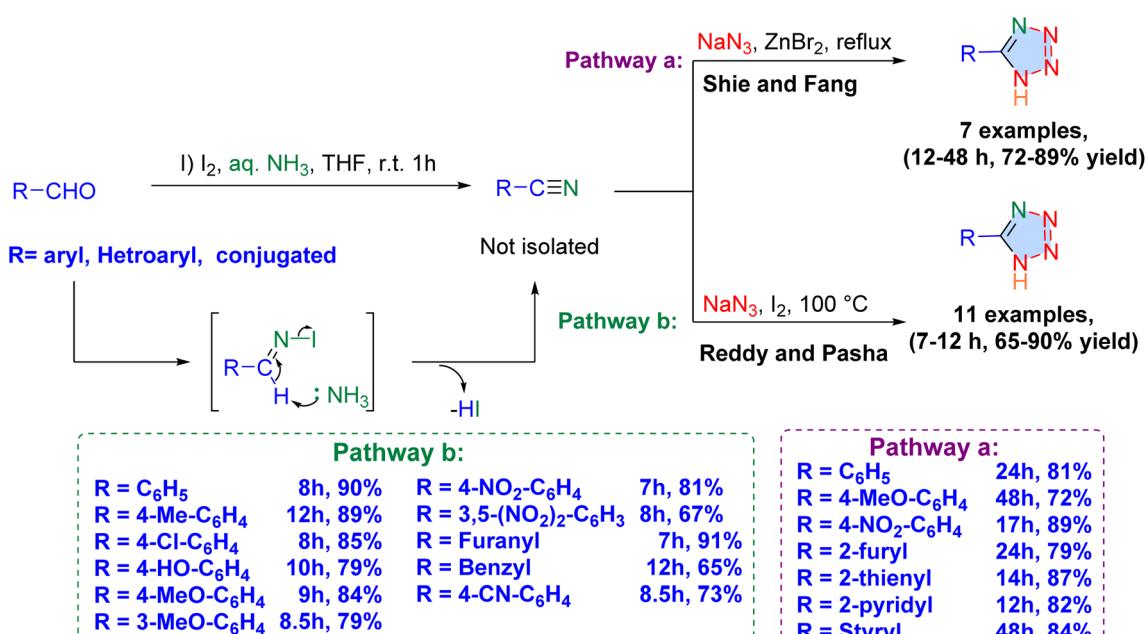


Scheme 34 Humic acid-catalyzed synthesis of 5-substituted tetrazoles.

laborious workup. The process involves *in situ* oxime formation from aldehydes and hydroxylamine, followed by a [3 + 2] cycloaddition with hydrazoic acid generated under the reaction conditions. Mechanistic investigations, supported by intermediate isolation and control experiments, confirmed the crucial role of the DMSO-HNO₃ combination in promoting these transformations. A broad scope of aromatic aldehydes was tolerated, affording tetrazoles in excellent yields (up to 97%), with both electron-donating and electron-withdrawing substituents performing efficiently. Limitations were noted with acid-sensitive substrates such as furfural, while cinnamaldehyde gave only moderate yields, suggesting some substrate dependency.

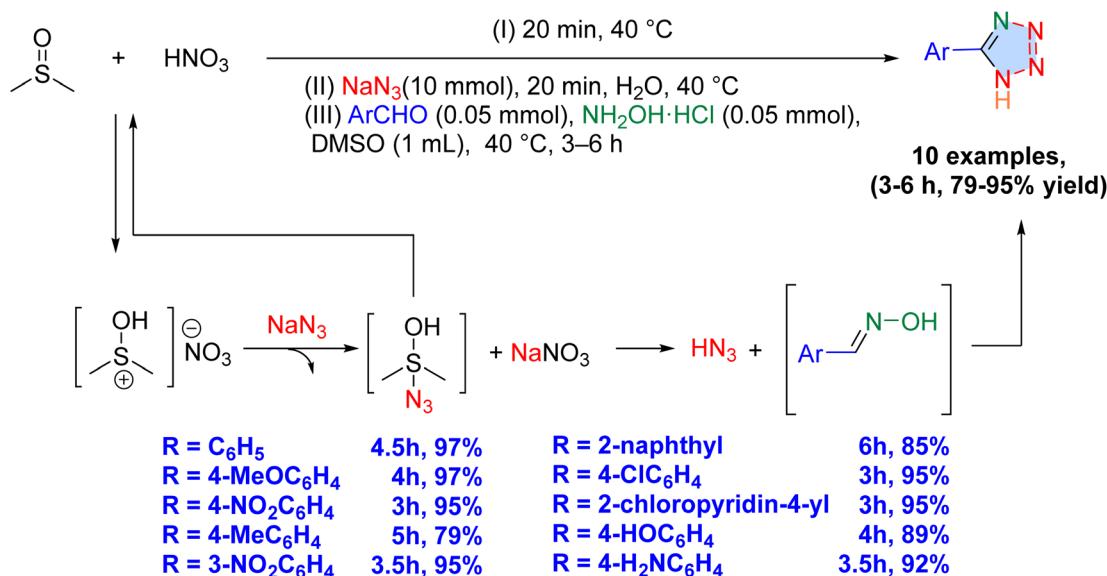
In 2022 Jasim *et al.* reported a sustainable and catalyst-free protocol for the synthesis of 5- and 1-substituted tetrazoles using TAIm[I] ionic liquid as a reaction medium under microwave and ultrasonic irradiation (Scheme 38).⁶⁵ The method exploits the facile exchange of iodide with azide to generate TAIm[N₃], which serves both as solvent and active reagent. This dual functionality eliminates the need for external catalysts or solvents, offering a greener and cost-effective approach. The

protocol efficiently transformed aldehydes, nitriles, and amines into the corresponding tetrazoles with high to excellent yields (up to 98%). Notably, microwave irradiation significantly reduced reaction times (30–90 min) compared to ultrasound (3–6 h), while maintaining comparable productivities. Both electron-donating and electron-withdrawing substituents on the aromatic precursors were well tolerated, demonstrating that electronic effects exerted minimal influence on the outcome. Even sterically hindered substrates provided satisfactory yields, underscoring the robustness of the method. A key advantage of this system is its recyclability: the ionic liquid could be reused for at least six consecutive cycles with negligible loss of efficiency, highlighting its stability under irradiation. Mechanistic studies suggested that the azide counter ion directly participates in tetrazole ring formation, while the ionic liquid matrix efficiently transmits microwave and ultrasonic energy to the reactants, effectively mimicking catalytic behavior. Compared with conventional transition-metal or heterogeneous ionic liquid systems, this method avoids metal leaching, toxic solvents, and extended reaction times, offering a more sustainable alternative. Overall, the TAIm[N₃]-mediated

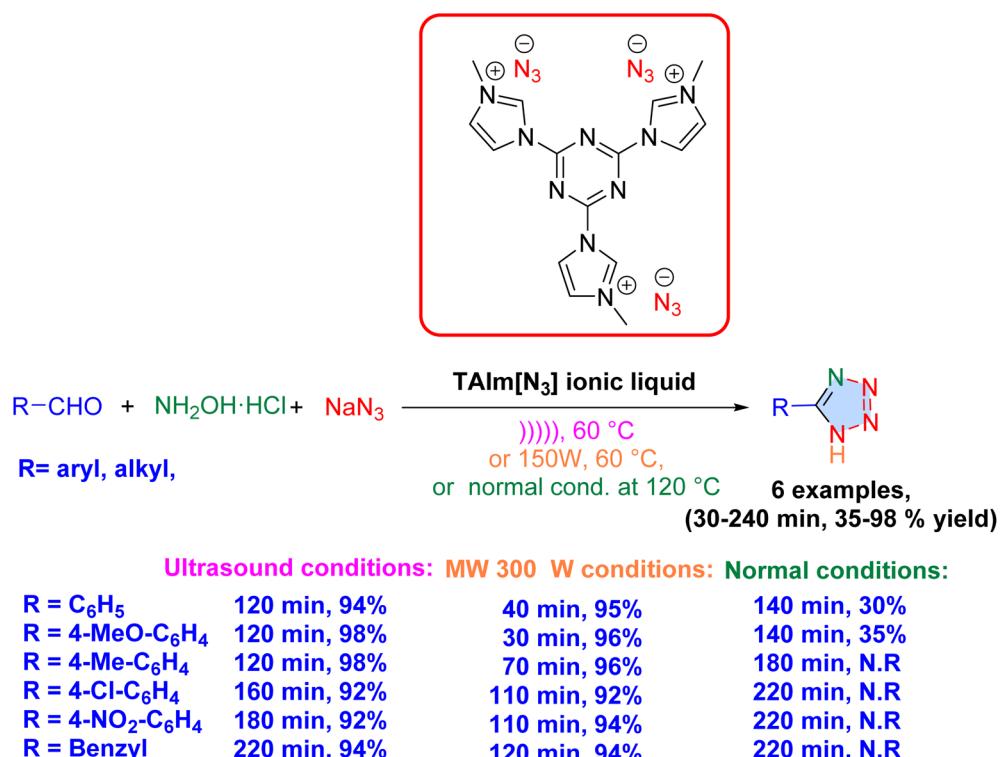
**NiFe₂O₄@CA@MIL-53(Fe)@CQDs-SO₃H**Scheme 35 NiFe₂O₄@CA@MIL-53(Fe)@CQDs-SO₃H catalyzed synthesis of 5-substituted tetrazoles and 4-aryl-1,2,3-triazoles.

Scheme 36 Direct conversion of aldehydes to tetrazoles in aqueous media by one-pot tandem reactions.





Scheme 37 One-pot preparation of 5-substituted 1H -tetrazoles from aldehydes by using a mixture of DMSO and HNO_3 in the presence of $\text{NH}_2\text{OH}\cdot\text{HCl}$ and NaN_3 .



Scheme 38 Synthesis of 5-substituted 1H -tetrazole in the presence of TAIm[N₃] under microwave or ultrasound irradiations in comparison with normal conditions.

approach represents a versatile, eco-friendly, and scalable strategy for preparing pharmaceutically and industrially relevant tetrazoles, adding significantly to the growing body of green synthetic methodologies for nitrogen-rich heterocycles.

3. Conclusion

In conclusion, the synthesis of 5-substituted 1H -tetrazoles has undergone a significant evolution, with the emergence of diverse and innovative catalytic methodologies. These advancements offer considerable improvements in efficiency,

atom economy, and sustainability, highlighting the power of modern synthetic chemistry. The field has moved beyond classical nitrile–azide cycloadditions and stepwise routes from alcohols, aldehydes, and oximes, which often relied on reactions like the Sandmeyer and Rosenmund–von Braun. Instead, there has been a clear shift toward streamlined, one-pot, aldehyde-based multicomponent reactions. The use of transition-metal complexes, magnetic nanocatalysts, ionic liquids, and biomass-derived platforms in these reactions reflects a growing commitment to green chemistry principles. The impressive variety of these aldehyde-based methodologies, combined with their broad substrate scope and operational simplicity, establishes them as the most practical and sustainable approach for constructing tetrazole rings. Future research should prioritize enhancing catalyst recyclability, improving scalability, and designing metal-free or bio-derived catalytic systems to further improve environmental compatibility. Such efforts will undoubtedly expand the utility of 5-substituted 1*H*-tetrazoles and solidify their importance in pharmaceuticals, energetic materials, and various advanced functional applications.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results have been included, and no new data has been generated as part of this review.

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