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ADVANCES IN GREEN CATALYSIS BASED ON METAL OXIDES FOR THE SYNTHESIS OF N-HETEROCYCLES

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ABSTRACT:

An environmentally friendly substitute for conventional techniques, green catalysis with metal oxides has become a viable approach for the sustainable synthesis of N-heterocycles. This study highlights the critical role that metal oxides play in facilitating effective and environmentally benign N-Heterocycle synthesis by offering a thorough summary of current developments in the field. The investigation of catalytic processes that reduce waste generation and energy consumption has been spurred by the pressing need for sustainable practices in organic synthesis, motivated by environmental concerns. The introduction stresses the limitations of traditional synthetic techniques while highlighting the importance of N-heterocycles in medicines and other industrial uses. Because of their availability, low toxicity, and variety of catalytic activity, metal oxides have gained interest as catalysts. The mechanistic aspects of N-heterocycle synthesis are explained through a review of key reactions, which illustrate how metal oxides catalyse transformations that are essential for the production of various N-heterocyclic structures. The efficiency of metal oxides in mediating these processes is demonstrated by recent research, which show improved selectivity and yield in comparison to conventional catalysts.

The use of metal oxides in multicomponent reactions to generate N-heterocycles has gained traction in green synthesis. By using numerous starting materials at once, MCRs provide atom-economic methods that streamline synthetic approaches and reduce waste. The review highlights the adaptability of this strategy for gaining access to a broad range of N-Heterocyclic scaffolds by presenting case examples of successful MCRs catalysed by metal oxides. The section on future perspectives delineates prospective directions for further investigation, with a focus on creating new metal oxide catalysts, refining reaction conditions, and investigating inventive synthetic approaches. The main results are outlined in the conclusion, which also highlights the revolutionary effect of green catalysis using metal oxides on N-Heterocycle synthesis and opens the door to ecologically friendly and sustainable methods in organic chemistry.

KEYWORDS: Green Catalysis, Metal Oxides, N-Heterocycles, Multicomponent Reactions, Sustainable Synthesis.

INTRODUCTION:

The synthesis of N-heterocycles represents a crucial facet of modern organic chemistry, finding applications in medicinal chemistry, materials science, and various industrial processes [i].These heterocyclic compounds, containing at least one nitrogen atom within the ring structure, exhibit diverse and often enhanced biological and chemical activities [ii]. However, the conventional methods employed for their synthesis often involve hazardous reagents, produce considerable waste, and demand high energy input, raising environmental and sustainability concerns. In response to these challenges, the field of catalysis has witnessed a paradigm shift towards more environmentally friendly practices [iii]. Among the various catalytic approaches, green catalysis has emerged as a promising avenue, emphasizing the use of non-toxic, renewable, and environmentally benign catalysts [iv].

The concept of green catalysis represents a transformative approach in the field of chemistry, emphasizing the integration of environmentally conscious principles into synthetic methodologies [v]. Green catalysis strives to minimize the ecological footprint associated with chemical processes by employing catalysts that are non-toxic, renewable, and promote atom efficiency. At its core, this paradigm shift is deeply rooted in the broader goals of sustainable chemistry, acknowledging the imperative to develop methodologies that are not only efficient in producing desired compounds but also considerate of the environmental impact [vi]. Green catalysis aligns with the principles of sustainable development by reducing waste generation, utilizing renewable resources, and mitigating the use of hazardous reagents, thereby contributing to a more ecologically balanced and economically viable future for chemical synthesis [vii].The importance of green catalysis becomes particularly pronounced in the broader context of sustainable chemistry, where the design and execution of chemical processes are scrutinized for their ecological implications [viii]. As industries and research communities increasingly recognize the urgency of adopting environmentally friendly practices, green catalysis emerges as a pivotal player in driving this transition. By fostering the development of cleaner and more sustainable methodologies, green catalysis not only addresses the pressing environmental concerns associated with traditional chemical processes but also lays the foundation for a more responsible and ecologically harmonious future in the realm of synthetic chemistry [ix].

The significance of N-heterocycles spans across various industries, with a notable impact in pharmaceuticals, agrochemicals, and materials science [x,xi]. In the pharmaceutical sector, N-heterocycles serve as fundamental building blocks for a myriad of drug molecules, influencing their pharmacological properties and therapeutic efficacy. The inclusion of nitrogen atoms within the heterocyclic structure often imparts unique biological activities, making these compounds essential in the design and synthesis of a wide array of pharmaceutical agents [xii]. From anti-cancer drugs to antibiotics and antiviral medications, the diverse applications of N-heterocycles underscore their indispensable role in the development of novel therapeutics [xiii, xiv]. Beyond the realm of pharmaceuticals, N-heterocycles play a crucial role in agrochemicals, contributing to the synthesis of pesticides, herbicides, and fungicides [xv, xvi]. The incorporation of these heterocyclic motifs in agrochemical formulations enhances their specificity and effectiveness in targeting pests and diseases, thereby bolstering agricultural productivity [xvii].Moreover, N-heterocyclic find applications in materials science, where their unique electronic and structural properties are harnessed for the design and fabrication of advanced materials. The versatility of N-heterocycles in diverse industrial sectors reflects their status as pivotal chemical entities, driving innovation and progress across the pharmaceutical, agricultural, and materials industries[xviii].

The challenges associated with traditional synthesis methods, characterized by harsh conditions, the use of toxic reagents, and the generation of substantial waste, underscore the pressing need for environmentally friendly alternatives in the synthesis of N-heterocyclic [xix]. As we explore the role of metal oxides in green catalysis within our review, these challenges become pivotal focal points. The conventional methods not only pose risks to the environment but also highlight the urgency for adopting cleaner, sustainable, and more efficient synthetic routes. Our review seeks to address these challenges by delving into the advancements offered by metal oxide-based green catalysis, positioning it as a promising solution for overcoming the environmental drawbacks associated with traditional N-Heterocycle synthesis methods. In doing so, we contribute to the broader narrative of advancing sustainable practices within the field of chemical synthesis [xx].

Introducing metal oxides as catalysts in the realm of green catalysis is pivotal for understanding their significant role in fostering environmentally sustainable synthetic methodologies [xxi]. Metal oxides, compounds composed of metal cations bonded to oxygen anions, bring forth a myriad of advantages that align seamlessly with the principles of green chemistry. Notably abundant and accessible, metal oxides such as titanium dioxide (TiO_2), zinc oxide (ZnO), and cerium oxide (CeO_2) provide economically viable and environmentally benign catalyst options, reflecting the essence of sustainability in their utilization[xxii]. Their low toxicity further enhances the safety of the synthesis process and the resulting products, contributing to the overall eco-friendliness of green catalysis. Beyond their abundance and safety profile, metal oxides exhibit diverse catalytic activities, making them versatile players in various types of reactions associated with green synthesis [xxiii]. Particularly noteworthy are their redox properties, a critical aspect in catalysing oxidation and reduction reactions, which are integral to the synthesis of N-heterocycles. Furthermore, the catalytic efficiency of metal oxides, enabling reactions under milder conditions, aligns harmoniously with the overarching green chemistry principle of optimizing processes for energy efficiency [xxiv]. The introduction of metal oxides as catalysts in green catalysis sets the stage for a comprehensive exploration of their specific applications, mechanisms, and contributions to advancing more sustainable and eco-friendly synthetic routes, with a particular focus on N-Heterocycle synthesis [xxv].

REACTIONS INVOLVED:

Heterocycles, characterized by the number and positioning of nitrogen atoms in their five-membered rings, are classified into distinct categories such as pyrroles, pyrazoles, imidazoles, and triazoles[xxvi]. This categorization sets the stage for exploring their synthetic pathways, with a particular focus on the utilization of various mixed oxides as catalysts or catalyst supports. The subsequent sections provide an in-depth examination of these heterocycles' facile synthetic routes, shedding light on how different mixed oxides play a crucial role in achieving impressive product yields within remarkably short reaction times [xxvii]. This discussion emphasizes the catalytic effectiveness of mixed oxides and their significance in facilitating efficient and rapid synthesis of heterocyclic compounds [xxviii,xxix].

Pyrroles:

The versatility of pyrroles, with their vast potential for diverse and impactful molecules, makes them a prized compound class in both medicinal and synthetic chemistry[xxx]. Their presence in numerous natural products further underscores their significance in the realm of biology. Among these pyrrole-containing alkaloids, a distinct tetracyclic ring structure is prevalent [xxxi].

This review explores the benefits of a novel catalyst system, $Fe_3O_4@SiO_2$ nanoparticles functionalized with an ionic liquid (1-methyl-3-(3-trimethoxysilylpropyl)-1H-imidazol-3-ium chloride), for the efficient synthesis of 1, 3-thiazolidin-4-ones. The prepared catalyst, $MNP@SiO_2$ -IL, was synthesized by treating $Fe_3O_4@SiO_2$ nanoparticles with the ionic liquid under specific conditions [xxxii]. Its catalytic performance was then evaluated in a three-component reaction involving various aldehydes, anilines, and thioglycolic acid, conducted under solvent-free conditions at 70°C. $MNP@SiO_2$ -IL demonstrated exceptional efficiency, affording high yields (86-94%) within concise reaction times (55-70 minutes), establishing a convenient and economical protocol. (Fig:1) Notably, the catalyst's magnetic properties facilitate its simple recovery and enable reusability[xxxiii].

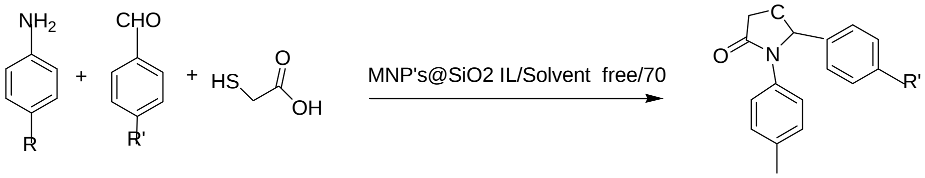

Figure 1:MNP@SiO$_2$ -IL: An Efficient Heterogeneous Catalyst for 1, 3-Thiazolidine-4-one Synthesis (Azgomi, N., & Mokhtary, M. (2015) [34]

Researchers have unveiled a ground-breaking method for synthesizing pyrroles with remarkable efficiency. This innovative strategy relies on a potent catalyst system and a streamlined three-component reaction[xxxv]. Through meticulous exploration of diverse low-valent titanium systems, the team identified three equivalents of the $TiCl_4$/Sm reagent as the sweet spot for generating an array of pyrrole derivatives [xxxvi]. (Fig: 2) Remarkably, the reaction flourishes at room temperature in anhydrous tetrahydrofuran, delivering impressive yields within a mere 15 minutes [xxxvii]. This rapid and facile protocol opens doors for the construction of a wide variety of regio-isomeric pyrroles [xxxviii]. Further showcasing the method's versatility, the authors successfully extended it to encompass both aromatic and aliphatic aldehydes and amines, granting access to a plethora of biologically relevant pyrrole products [xxxix].

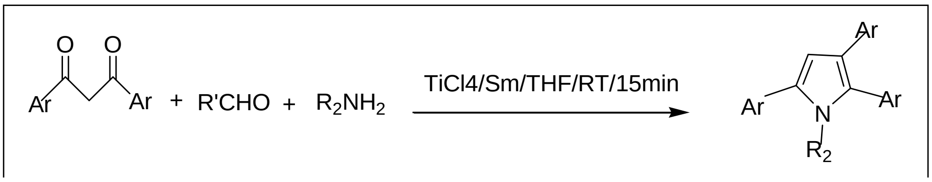

Figure 2:Synthesis of Polysubstituted pyrroles derivatives. (Dou, G., Shi, C., & Shi, D. (2008)[xi]

The five-membered pyrazole ring, composed of three carbon atoms and two adjacent nitrogen atoms, boasts a rich history dating back to its first synthesis by Knorr. This discovery paved the way for the development of antipyrine and its derivatives, establishing pyrazoles as a crucial group of heterocyclic compounds [xli]. Their versatility in metal chelation and extraction makes them invaluable tools in various scientific fields. They also serve as an enticing platform for combinatorial chemistry, [xlii] leading to a cascade of condensed heterocyclic systems with diverse medicinal and agricultural applications the impressive range of biological activities exhibited by pyrazoles cements their prominence among heterocyclic compounds [xliii]. They display potent antibacterial antifungal herbicidal and antiviral properties Notably, their pharmacological versatility extends beyond these areas, encompassing antiarrhythmic sedative and anti-inflammatory properties Furthermore, pyrazolines and annelated pyrazoles showcase remarkable antimicrobial activity N-substituted pyrazole derivatives hold promise in inhibiting and deactivating liver alcohol dehydrogenase[xliv]. Additionally, difenamizole and metamizole boast superior analgesic activity to aspirin Strategic fluorine incorporation, particularly through trifluoromethylation, plays a crucial role in enhancing the pharmaceutical and agrochemical potential of heterocyclic compounds[xlv]. This is particularly true for fluorinated pyrazoles, which exhibit exceptional biological activity as herbicides, fungicides, insecticides, and analgesics [xlvi].

Pyrazoles:

Akondi et al. developed a green and efficient method for synthesizing 1H-3-pyrazolones using a CeO_2 /SiO_2 catalyst. This four-component condensation relied on readily available starting materials like phenylhydrazine, β-keto ester, 2-naphthol, and aromatic aldehydes, with water as the sole solvent [xlvii]. Their key innovation was the creation of a novel Ce/SiO_2 complex through a sol-gel process, acting as a potent heterogeneous Lewis acid catalyst. (Fig:3). This catalyst offered several advantages: Excellent selectivity for the desired product, environmentally friendly, non-corrosive, and easily recyclable, Simple operation and low cost, Easy isolation, and recovery of the catalyst. Overall, the Ce/SiO_2 catalyst showcased its potential as a practical and sustainable tool for pyrazole synthesis [xlviii].

Maddila et al.'s study unveiled a promising method for efficiently producing a variety of pyrazole-4-carbonitrile derivatives, relying on a strategically designed CuO/ZrO_2 catalyst. This three-component Mannich-type reaction, utilizing readily available starting materials like phenylhydrazine, malononitrile, and assorted aromatic aldehydes, impressively delivered good to excellent yields within a short two-hour timeframe. The key to this success lies in the researchers' ingenious creation of the mixed oxide catalyst through a simple wet-impregnation technique. This resulted in a catalyst boasting remarkable activity, surpassing existing options in its efficiency. Furthermore, its impressive durability shone through its reusability over five cycles, maintaining consistently high performance without significant decline. In essence, the CuO/ZrO_2 catalyst's combination of efficacy, reusability, and ease of preparation establishes it as a valuable tool for synthesizing a diverse range of pyrazole-4-carbonitrile derivatives [xlix].

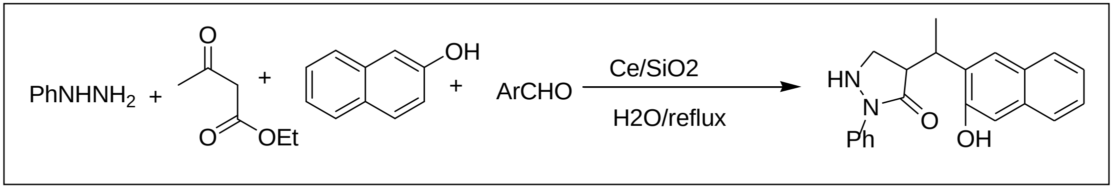

Figure 3: Reaction of 1H-3-pyrazolones synthesis.

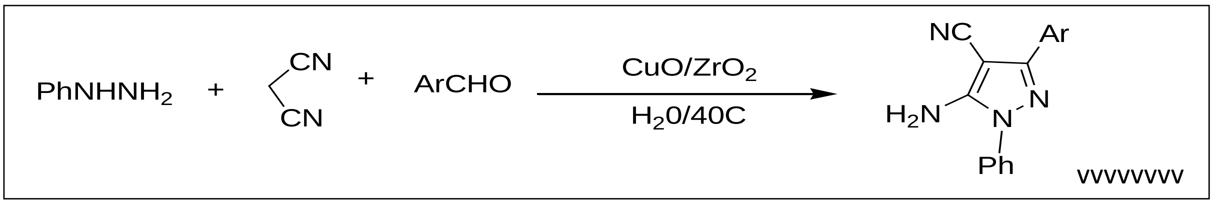

Figure 4: Reaction of pyrazole-4-carbonitrile.

Imidazole’s:

With its signature formula $C_3H_4N_2$ and fascinating dual nature, imidazole shines as a captivating member of the aromatic heterocycle family, boasting distinct alkaloid properties. While the term "imidazole" denotes the parent compound, imidazoles collectively represent a class of heterocycles sharing a similar ring structure but exhibiting variations in substituents. This distinctive ring system plays a pivotal role in numerous biological building blocks, including histidine and the related hormone histamine. Imidazole possesses the dual capability to function as both a base and a weak acid, contributing to its versatility. Notably, this heterocyclic structure is a fundamental component in various drugs, such as antifungal agents and nitroimidazoles[l].

In the context of catalysis, CuO in Fe_3O_4 nanoparticles has been employed as Lewis’s acids, effectively activating carbonyl groups in aldehydes for nucleophilic attacks. The incorporation of $CuFe_3O_4$ magnetic nano mixed oxide catalysts introduces a practical aspect to the catalytic process, as these can be easily isolated and recycled using an external magnet [li]. Leveraging the accessible surface area of nonporous magnetic nanoparticles enhances the catalytic performance of this system. Specifically, their research demonstrated that these nanoparticles could catalyze the cyclic condensation reaction involving aldehyde, benzyl, propargylamine, and ammonium acetate (NH_4OAc) in a mixture of aqueous ethanol, yielding high yields of 1,2,4,5-tetrasubstituted imidazole derivatives. (Fig: 5) The appealing features of this catalytic process include its simplicity in workup, a short reaction duration, and the catalyst's high reusability, making it an attractive tool in synthetic applications[lii].

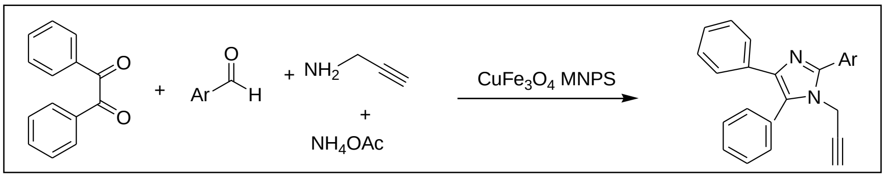

Figure 5: Formation of imidazoles.

Microwave irradiation proved to be a powerful tool for synthesizing 1,2,4,5-tetrasubstituted-1H-imidazoles. Combining readily available starting materials like aldehydes, benzil, primary amines, and NH_4OAc with a novel silica-supported $SbCl_3$ catalyst ($SbCl_3/SiO_2$), the reaction readily delivered good to excellent yields within a mere 15 minutes (Fig:6). This unique mixed oxide catalyst, conveniently prepared as a simple mechanical mixture of $SbCl_3$ and silica, shines for its efficiency and ease of application in this solvent-free process. By demonstrating impressive activity and operational simplicity, $SbCl_3/SiO_2$ paves the way for a promising approach to generate a diverse range of rapidly and efficiently 1,2,4,5-tetrasubstituted-1H-imidazoles[liii,liv].

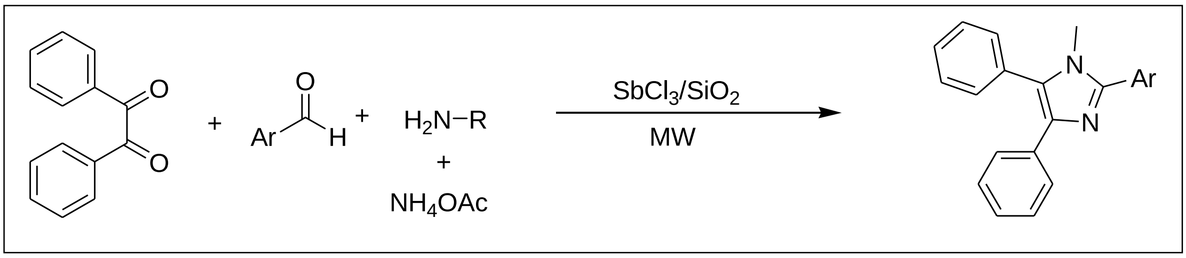

Figure 6: Synthesis of substituted imidazole's

Triazoles:

Due to their unique three-nitrogen arrangement, triazole derivatives form a vital class of organic heterocycles boasting diverse pharmacological applications. From antibacterial and antifungal activity to herbicidal and antiviral properties, they hold immense potential for drug development. Notably, some derivatives even exhibit antiarrhythmic, sedative, hypoglycaemic, and anti-inflammatory effects[lv]. In a recent study, Saeed et al. presented a powerful copper-(II)-1,4-dihydroxyanthraquinone catalyst anchored onto superparamagnetic $Fe_3O_4@SiO_2$ nanoparticles. They employed an ion-pair strategy to immobilize the catalyst onto the silica-coated iron oxide, creating the Cu (II)-DAQ$Fe_3O_4@SiO_2$ system[lvi]. (Fig:7) This innovative mixed oxide catalyst demonstrated remarkable selectivity in a three-component reaction involving alkyne, aryl boronic acid, and sodium azide, generating 1-aryl-1,2,3-triazole derivatives in water-acetonitrile[lvii]. One of the key strengths of this method lies in its green chemistry approach. Eliminating the need for harmful surfactants, toxic reagents, and organic solvents simplifies the purification process and minimizes environmental impact. Additionally, the magnetically recoverable catalyst showcases impressive reusability, maintaining its catalytic activity for at least six reaction cycles without significant decline.[58]

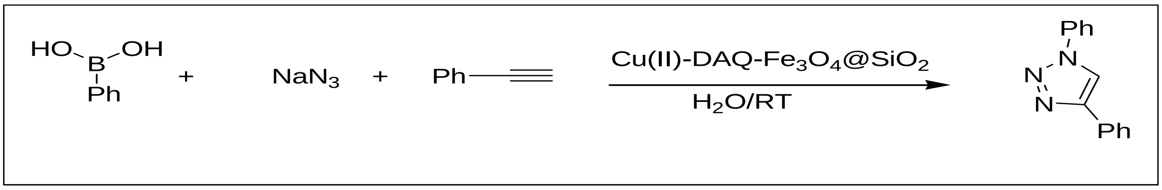

Figure 7. Rection of 1-aryl-1,2,3-triazole synthesis

Beyond Fe_3O_4 Nano catalysts, the realm of Cu-functionalized renewable catalysts expands to encompass both $CuFe_2O_4$ mixed oxide nanoparticles and $CoFe_2O_4$ magnetic Nano catalysts as viable magnetic supports. Illustrating this versatility, Kumar et al. (2012) demonstrated the impressive activity and reusability of a $CuFe_2O_4$ 4 mixed oxide catalyst in alkyne-azide cycloaddition reactions, culminating in the efficient synthesis of 1,4-disubstituted-1,2,3-triazoles.(Fig:8)This single-pot, multicomponent strategy leveraged the in-situ formation of benzyl azides from substituted benzyl halides and NaN_3, followed by their facile coupling with alkynes in water solvent, leading to excellent yields. Further showcasing the adaptability of $CuFe_2O_4$ Nano catalysts, Kumar et al. also reported a one-pot cycloaddition approach for synthesizing 1, 4-diaryl-1,2,3-triazole derivatives from acetylenes, sodium azide, and boronic acid. (Fig:9)

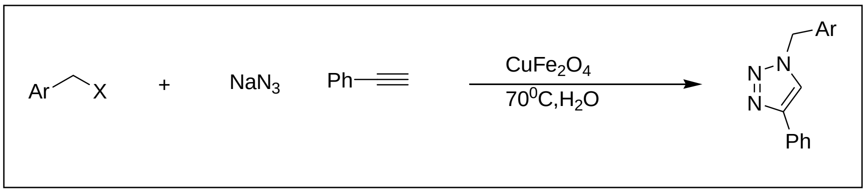

Figure 8:Synthesis of triazoles using $CuFe_2O_4$

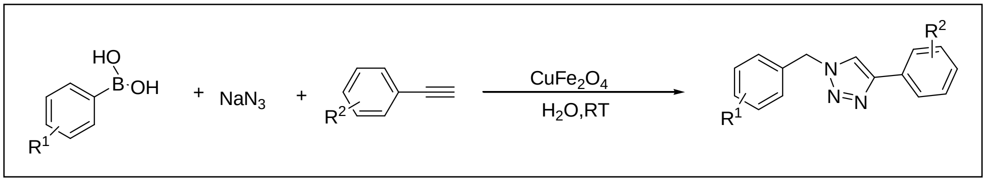

Figure 9: One pot formation reaction of 1,4-aryl-1,2,3-triazoles

Reactions involved in the synthesis of Six-membered ring heterocycles:

The two principal types of six-membered heterocycles, pyridines, and pyrimidines, differ solely in the number of nitrogen atoms incorporated into their aromatic rings. For their diverse heterocyclic syntheses, researchers have explored a multitude of methodologies employing various heterogeneous catalysts, including zeolites, mixed oxides, and others [lx]. Among these, mixed oxides have garnered significant attention due to their advantageous combination of cost-effectiveness, facile preparation, and excellent recyclability. This has spurred their successful deployment in the efficient production of a diverse array of six-membered heterocycles, often delivering good to excellent yields. The following sections delve deeper into the exciting realms of efficient pyridine and pyrimidine synthesis, spearheaded by the innovative applications of various mixed oxide catalyst materials [lxi].

Pyridines:

Pyridines, distinguished by their single nitrogen atom embedded within a six-membered aromatic ring, hold a prominent position among single-nitrogen heterocycles. Pioneered by Thomas Anderson's landmark synthesis in 1849, the exploration of this diverse family has revealed a treasure trove of pyridine derivatives showcasing a remarkable range of pharmacological activities. From taming inflammation and combating viral infections to alleviating pain and curbing neoplastic growth, these versatile molecules offer promising avenues for tackling various medical challenges. Moreover, their antifungal, antioxidant, and insecticidal properties extend their potential beyond human health, hinting at their valuable contributions to protecting crops and controlling pests. This impressive breadth of biological functions underscores the rich potential of pyridine derivatives and necessitates further investigation into their diverse therapeutic and agrochemical applications [lxii].

The quest for diverse pyridine derivatives with potential biological activities has driven immense research interest. In this domain, Dam et al. made a significant contribution by developing a one-pot, multicomponent reaction for the synthesis of 1,4-dihydropyridine (1,4-DHP) derivatives[lxiii].This streamlined approach utilizes readily available aldehydes, dimedone or 4-hydroxy coumarin, and NH_4OAc as reactants, combined with the catalytic prowess of $Fe_3O_4@SiO_2$ mixed oxide nanoparticles in a sustainable water solvent. Remarkably, the protocol delivers a broad spectrum of substituted 1,4-DHPs with impressive yields ranging from 82% to 95%. The reactions proceed swiftly under reflux conditions, reaching completion within a mere 10-30 minutes, further highlighting the efficiency of this novel methodology [lxiv].

The co-precipitation method, employing ferric nitrate and ferrous sulfate in an ammonia solution, served as the foundation for the synthesis of ferrate nanoparticles, the core component of the $Fe_3O_4@SiO_2$ mixed oxide catalyst. To augment the chemical and thermal stability of these ferrate particles, a SiO_2 shell was meticulously deposited via NH_3-catalyzed hydrolysis of a precursor silicate[lxv](Fig:10).Transmission electron microscopy (TEM) analysis unveiled the refined architecture of the resulting $Fe_3O_4@SiO_2$ catalyst, showcasing a well-defined structure with a dark spherical metal particle core embraced by a distinct SiO_2 core-shell configuration[lxvi].

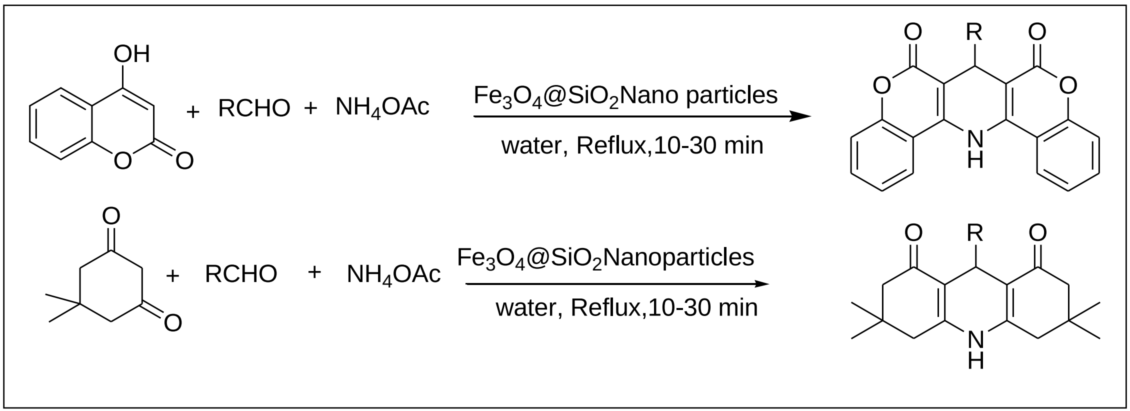

Figure 10. Synthesis of 1,4-DHPs

Pyrimidines:

The six-membered ring of pyrimidine, a nitrogen-packed heterocycle ($C_4H_4N_2$), holds immense potential as a building block for valuable chemicals. From medicine to industry and agriculture, its diverse derivatives unlock a treasure trove of applications[lxvii].In a recent feat of chemical ingenuity, Naeimi and colleagues unveiled a novel one-pot, multicomponent reaction for crafting intricate pyrido-dipyrimidines. This streamlined process relies on the dynamic trio of 2-thiobarbituric acid, aromatic aldehydes, and NH_4OAc, all guided by the magic touch of $CuFe_2O_4$ mixed oxide nanoparticles, a Lewis acid catalyst[lxviii].Green chemistry takes center stage here, with water playing the role of the solvent under the gentle nudge of microwave-assisted heating(fig:11). The rewards are impressive – high yields, ranging from good to excellent, showcase the power of this innovative approach [lxix].

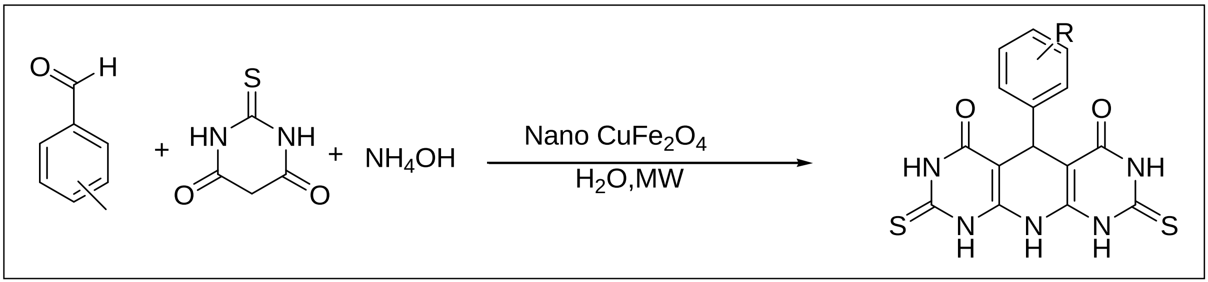

Figure:11-Reaction of novel pyrido-dipyrimidine synthesis.

The $CuFe_2O_4$ catalyst was synthesized via a co-precipitation method, resulting in a material with pronounced magnetic properties. This approach, combining microwave-assisted heterocyclic synthesis with a readily recoverable catalyst, holds significant promise for enhancing reaction yields and shortening process times [lxx].

Building upon the promise of mixed oxide magnetic nanocatalysts, Shaterian and Aghakhanizadeh designed two innovative options in their study. They employed 3-aminopropyltriethoxysilane (APTES) as a versatile support, crafting both APTES-supported SBA-15 and APTES-supported Fe_3O_4 nanocatalysts.(Fig:12) These novel materials were then put to the test in the solvent-free, room-temperature condensation of malononitrile, salicylaldehyde, and secondary amines. Impressively, the reaction yielded chromeno[2,3-d] pyrimidines with high efficiency, reaching yields between 87% and 93%. Further adding to their appeal, these catalysts boast excellent recuperability, facilitating their reuse in subsequent reaction cycles [lxxi].

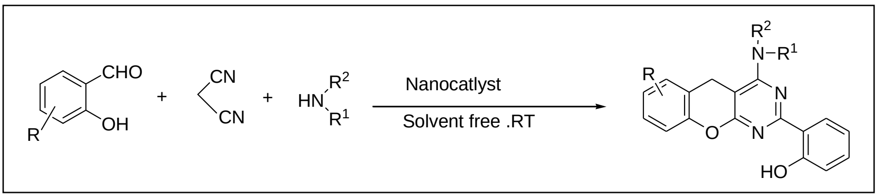

Figure:12-chromeno-[2,3-d] pyrimidines derivative's preparation

In a search for environmentally friendly approaches to synthesize 3,4-dihydropyrimidine-2(1H)-ones/thiones, Ghomi et al. turned to a novel mixed oxide catalyst. This catalyst, featuring nano silica-supported tin (II) chloride, facilitated the reaction of urea/thiourea, substituted aldehydes, and ethyl acetoacetate in a sustainable manner. Its preparation involved simply adding anhydrous $SnCl_2$ to a suspension of silica gel nanoparticles in dichloromethane. Analysis with powder X-ray diffraction revealed the catalyst's high crystallinity, evident in the sharp and intense peaks observed. Additionally, temperature-programmed desorption confirmed the presence of crucial Lewis acidic sites on the catalyst's surface (Fig:13).

Optimal reaction conditions, involving reflux at 78°C in ethanol with just 0.45 mol% of the catalyst, yielded outstanding results. The desired molecules were obtained in impressive quantities, ranging from 88% to 97%. Remarkably, even after five rounds of use, the catalyst held its own. Diffraction and SEM analysis confirmed its structural integrity, solidifying its potential as a robust and eco-friendly tool for heterocyclic synthesis [lxx].

Heteropolyacids have carved a niche for themselves as recyclable catalysts, proving their worth in organic transformations and the petrochemical industry. In a recent breakthrough, Valeria et al. successfully anchored $H_3PMo_{12}O_{40}$ onto the surface of silica-coated vanadia mixed oxide particles. These spherical catalysts, with a convenient size around 50 nm, showcased a significant advantage: a boost in active surface sites and uniform distribution, key factors in their enhanced catalytic performance. This advantage was put to the test in a one-pot multicomponent acid-condensation reaction. By bringing together benzaldehyde, ethyl trifluoroacetoacetate, and urea under solvent-free conditions, these clever catalysts produced substituted hexahydropyrimidine derivatives in impressive yields and within a brief timeframe [lxxiii](Fig:14).

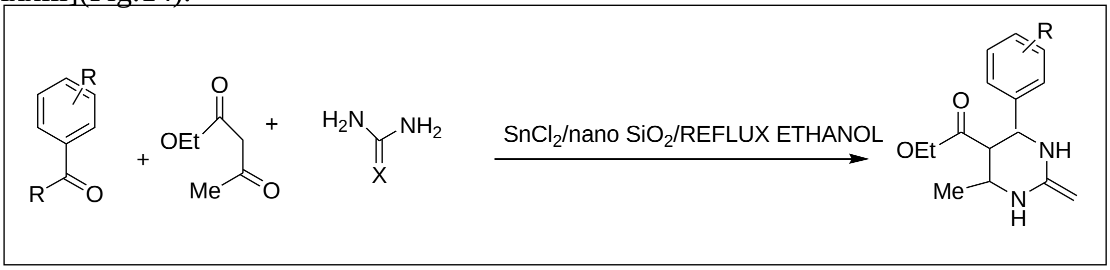

Figure :13-Reaction of Synthesis of dihydropyrimidine derivatives

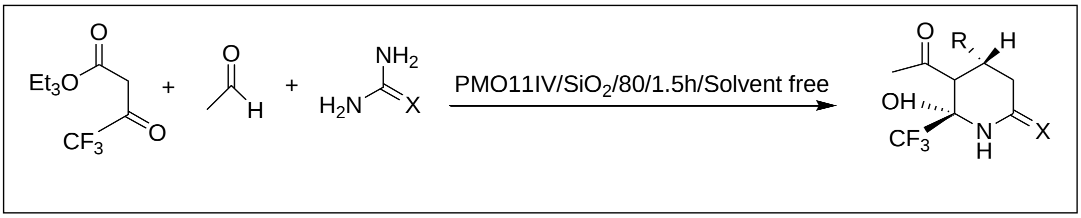

Figure:14-Synthesis of hexahydro pyrimidine

Types Of N-hetreocycles:					
5 membered	Furan	C_4H_4O	Aromatic, weakly basic; precursor for polymers and solvents	Furfural, used in food flavorings and resins	[lxxvi,lxxvii]
	Thiophene	C_4H_4S	Aromatic, weakly basic; building block for conducting polymers and pharmaceuticals	Tolfenal, a drug for asthma and allergies	[lxxviii,lxxiv]
	Imidazole	$C_3H_4N_2$	Aromatic, basic; core structure of many pharmaceuticals and catalysts	Histamine, a key molecule in allergic reactions	[lxxx]
	Oxazole	C_3H_3NO	Aromatic, weakly basic; found in natural products and used in pharmaceuticals and agrochemicals	Imidazole derivative, a potential anticancer agent	[lxxxi,lxxxii]
	Thiazole	C_3H_3NS	Aromatic, weakly basic; central scaffold for antibiotics and agrochemicals	Vitamin B1 (thiamine), is essential for energy metabolism	[lxxxiii, lxxxiv]
	Pyrazole	$C_3H_3N_2$	Aromatic, weakly basic; versatile scaffold in pharmaceuticals, agrochemicals, and dyes	Celecoxib (NSAID), rifabutin (antibiotic), tartrazine (yellow food dye)	[lxxxv. lxxxvi]
6-membered	Pyridine	C_5H_5N	Aromatic, basic; found in vitamins, drugs, and agrochemicals	Nicotine, the addictive component of tobacco	[lxxxvii, lxxxviii]
	Piperidine	$C_5H_{11}N$	Aliphatic, strong base; used in pharmaceuticals and organic synthesis	Piperine, the pungent compound in black pepper	[lxxxix,xc]

	Morpholine	C_4H_9NO	Aliphatic, strong base; found in pharmaceuticals and used as a cleaning agent	Morphine derivative, used in pain management	[xc]
	Quinoline	C_9H_7N	Aromatic, basic; core structure of antimalarial drugs and dyes	Quinine, a classic antimalarial medication	[xci.xcii]
	Isoquinoline	C_9H_7N	Aromatic, basic; found in alkaloids and used in pharmaceuticals and dyes	Papaverine, a muscle relaxant and vasodilator	[xciii.xciv]

FUTURE PROSPECTS AND CHALLENGES:

The future of green catalysis based on metal oxides for N-heterocycle synthesis presents exciting prospects and significant challenges. In terms of prospects, researchers are delving into the tailored design of metal oxides, exploring new compositions that possess optimized catalytic properties tailored for specific N-heterocycle synthesis[xcv]. This approach aims to enhance efficiency and selectivity in catalysis, offering a more precise and targeted methodology. Additionally, the investigation of nanostructured Metal oxide catalysts holds promise, as researchers explore their potential to improve surface area, reactivity, and overall catalytic performance in green synthesis[xcvi]. The development of metal oxide catalysts designed specifically for challenging N-heterocycle synthesis reactions is on the horizon, expanding the scope of feasible transformations. Sustainable synthesis routes are also a focal point, with efforts directed towards designing environmentally friendly pathways that minimize waste, energy consumption, and overall environmental impact. An in-depth mechanistic understanding of the intricate processes governing metal oxide-catalyzed N-heterocycle synthesis is crucial, facilitating more precise catalyst design and reaction optimization [xcvii, xcviii].

However, these prospects are accompanied by a set of challenges. Catalyst stability is a paramount concern, requiring solutions to address the stability and durability of metal oxide catalysts under various reaction conditions, especially in long-term and large-scale applications[xcix]. Achieving precise control over selectivity in multicomponent reactions is another challenge, demanding strategies to fine-tune catalytic processes for the desired N-heterocycle products while minimizing the formation of unwanted by-products. Adapting metal oxide-based catalytic processes for N-heterocycle synthesis to larger scales introduces challenges related to scalability, considering industrial requirements and economic feasibility [c].A comprehensive understanding of the complex reaction pathways and kinetics involved in metal oxide-catalyzed N-heterocycle synthesis is necessary for improved predictability and reproducibility. Efforts to develop efficient methods for the recovery and recycling of metal oxide catalysts are crucial, aiming to minimize environmental impact and ensure economic feasibility on an industrial scale[ci].Addressing challenges related to the biocompatibility of metal oxides in pharmaceutical applications is paramount, focusing on enhancing biocompatibility and minimizing potential toxicity[cii].Lastly, designing metal oxide catalysts that can effectively handle a broad range of substrates is essential for ensuring versatility in N-heterocycle synthesis. Navigating these prospects and challenges will be instrumental in advancing the field of green catalysis based on metal oxides for the synthesis of N-heterocycles, ultimately contributing to sustainable and efficient synthetic methodologies[ciii].

CONCLUSION:

The burgeoning field of green catalysis using metal oxides as catalysts holds immense promise for revolutionizing the synthesis of N-heterocycles. These versatile mixed oxides, already playing a pivotal role in diverse industries, demonstrate remarkable potential as heterogeneous catalysts, accounting for over 30% of industrially employed catalysts. Workhorses like SiO_2 , CeO_2 , ZrO_2 , TiO_2 , $Al_2 O_3$, and hydroxyapatites stand out as crucial catalyst supports. Strategically depositing active metals like Fe, Co, V, Mn, Cu, and Ni onto these oxide surfaces creates efficient catalytic sites, significantly impacting reaction selectivity. This focus on nitrogen-containing heterocycles, with their immense medicinal and agricultural applications, underscores the need for efficient and sustainable synthetic routes.

By strategically leveraging the synergistic interplay of multiple metal oxides, researchers have unlocked the potential for controlled Carbon-carbon bond formation in organic substrates. This breakthrough enables the development of novel pyrrole, pyrazole, and triazole derivatives through efficient multicomponent reactions. This one-pot approach, fueled by the versatility of mixed oxide catalysts, opens a vibrant frontier for engineering N-heterocycles with precisely tailored properties and expanded functionalities. However, deciphering the intricate orchestration of chemical reactions occurring on these dynamic catalyst surfaces remains a captivating scientific challenge. Bridging this knowledge gap holds immense promise for further refining and enriching the potential of mixed oxides, both as catalysts and catalyst supports. This continuous exploration paves the way for a flourishing future of green catalysis in N-heterocycle synthesis, propelling advancements in sustainable and targeted molecule design.

DECLARATION OF COMPETING INTEREST:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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