Exploring the Frontiers of Sustainability: A Review on Eco-Friendly Methods for the Synthesis of Novel Heterocyclic Compounds

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Abstract:

The quest for sustainable and environmentally benign methods for the synthesis of heterocyclic compounds has gained significant momentum in recent years. This review article provides a comprehensive overview of the latest developments in eco-friendly methods for the synthesis of novel heterocyclic compounds. We discuss the advantages and limitations of various green chemistry approaches, including microwave-assisted synthesis, ultrasound-assisted synthesis, solvent-free synthesis, and biocatalytic synthesis. Furthermore, we highlight the applications of these heterocyclic compounds in various fields, such as pharmaceuticals, agrochemicals, and materials science.

Introduction:

Heterocyclic compounds are an important class of organic molecules that play a vital role in various biological and chemical processes. They are widely used in pharmaceuticals, agrochemicals, and materials science due to their unique properties and reactivity. However, traditional methods for the synthesis of heterocyclic compounds often involve the use of toxic solvents, harsh reaction conditions, and hazardous reagents, which can have detrimental effects on the environment and human health.

Heterocyclic compounds containing nitrogen, oxygen and sulphur atom widely present in various natural products and biologically active molecules, functional materials, ligands and catalysts, and are also used as multipurpose building blocks in organic synthesis [1]. Particularly, many commercial medicines and agrochemicals possess heterocyclic moieties [2]. Substantial efforts

have been devoted into development of synthetic methods toward construction of heterocyclic compounds [3].In the continuation of our research program directed toward the development of new synthetic methods for the preparation of a variety of heterocyclic compounds via mild and environmentally benign conditions [4]. The concept of green chemistry has made significant impact on many frontages including the use of green solvents, bio-renewable resources and sustainable catalyst materials [5]. Environmentally benign protocols have been explored for heterocyclic synthesis to improve energy consumption, atom economy and reaction yields [6]. Designing the high efficiency reactions that work at room temperature and use of alternative energy sources has become an attractive choice. A radical evolution in the field of synthetic organic chemistry is the practice of multicomponent reactions (MCRs), which involve more than three reactants in one-pot reaction [7]. In addition to avoidance of separation and 4603 purification of intermediates, MCRs are generally environment friendly, selective, atom efficient and time saving [8]. Thus, MCR approach has gained significant popularity in the fields of pharmaceutical chemistry and drug development, including control of stereo isomers [9]. In the sequence of the reaction, inter coordination between the reactants, solvent and catalyst is crucial for the success of MCRs [10]. Consequently, with choice for diverse molecular entities as reactants, MCRs have cherished in the designing of different organic blocks to prepare various fascinating heterocyclic frameworks [11-12]. This review will summarize the reported protocols for the preparation of heterocyclic derivatives, but as mentioned, most reports this review covers the preparation of heterocyclic derivatives by multicomponent reactions using conventional conditions, MW, and ultrasonic irradiations from 2005 to 2020. The most multicomponent reactions (four-component) have been introduced different compounds.

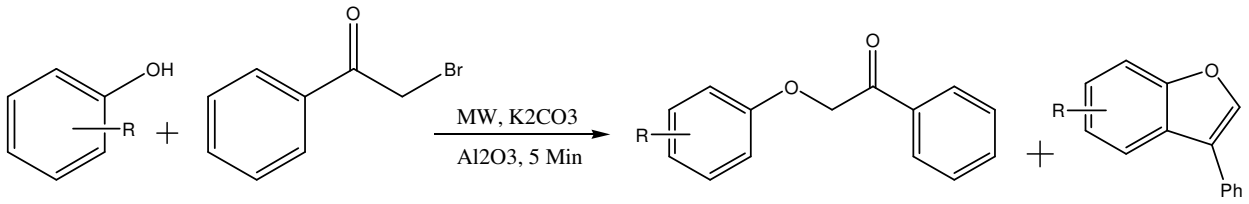
Green chemistry (GC) deals with application of a set of 12 principles to minimize the use and generation of hazardous and unwanted substances [13]. It is about minimization of the contact of humans and environment to hazardous chemicals [14]. Green chemistry comprises twelve principles proposed by Anastas and Warner for first time, which includes prevention of pollution, increasing atomic economy, using less hazardous chemicals, design of nontoxic chemicals, utilization of safer solvent and auxiliaries, design for energy efficiency, use of renewable feed stocks, reduce derivatives, use of effective catalyst, design for degradation, real-time analysis for pollution prevention and applying inherently safer chemistry for accident prevention Thus far, significant advances have been made in green synthesis of

pharmacologically important heterocycles [15] and these achievements include using solvents free or green solvents (preferably water), alternative reaction media, one-pot multicomponent reactions (MCRs), and effective recyclable magnetic nanoparticles

Eco-Friendly Methods for the Synthesis of Heterocyclic Compounds:

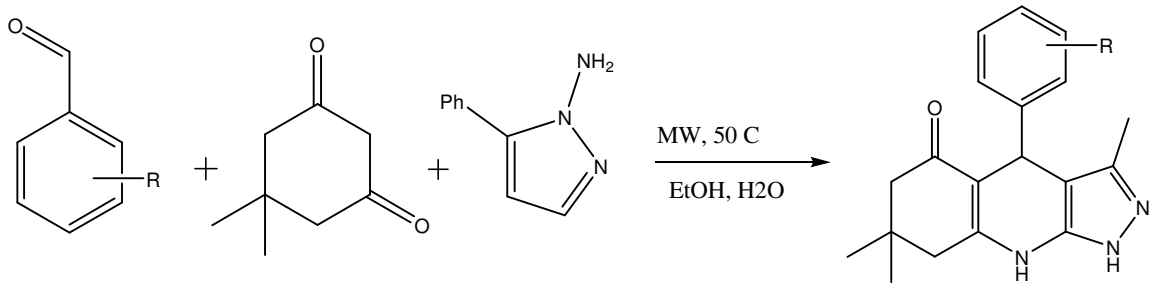
1. **Microwave-Assisted Synthesis:** Microwave-assisted synthesis has emerged as a powerful tool for the synthesis of heterocyclic compounds. This method offers several advantages, including rapid reaction rates, improved yields, and reduced solvent usage.

Wang et, al A one-pot synthesis of functionalized benzofurans was developed via O-alkylation, carbon–carbon coupling/cyclization, and dehydration olefination tandem reactions from phenols and phenacyl bromide. The reactions were carried out under microwave irradiation and solvent-free conditions in the presence of alumina supported inorganic bases. Formation of ethers asby-products were also reported (Scheme-1)[16].



Scheme-1: MW-assistedsolid-statesynthesisof3-phenylbenzofurans.

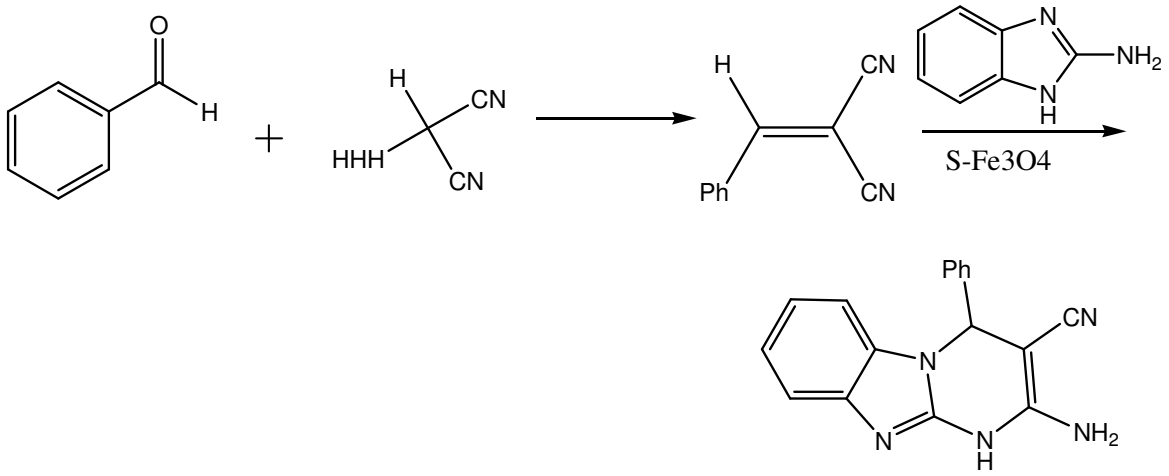
Khumalo and colleagues They used MW irradiation to synthesise eleven new pyrazolo-[3,4-b]-quinolines under catalyst-free and aqueous solvent conditions. Operational simplicity, a simple workup technique, mild conditions, fast reaction durations, high yields with excellent purity, and no column chromatography for compound purification are all important advantages of this protocol. To the best of our knowledge, this is the first publication describing the use of MW irradiation for the synthesis of pyrazolo-[3,4-b]quinoline derivatives in aqueous EtOH solvent. (scheme-2).The current technique will offer an alluring engineered convention for the planning of basically differed drug-like mixtures for the drug and medication plan disclosure fields [17].



Scheme -2 :pyrazolo-[3,4-b]-quinoline derivatives a three component green synthetic route

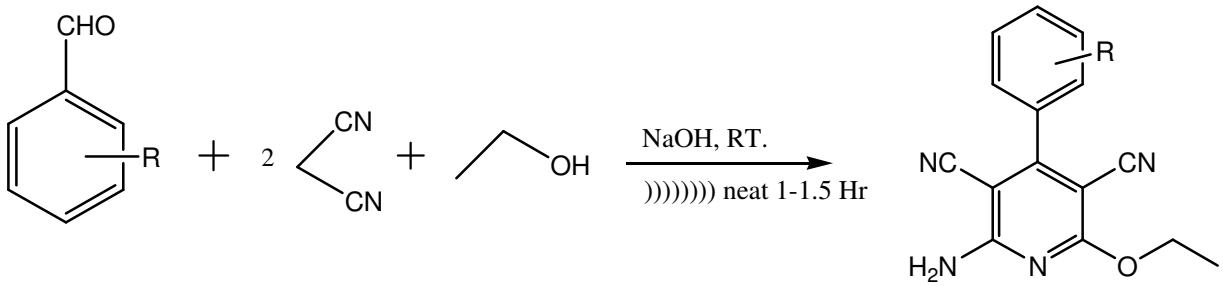
2. Ultrasound-Assisted Synthesis: Ultrasound-assisted synthesis is another eco-friendly method that has gained significant attention in recent years. This method uses high-frequency sound waves to accelerate chemical reactions, resulting in improved yields and reduced reaction times.

Pratibha et al, They have developed a simple and efficient ultrasound assisted multicomponent synthesis of the biologically active imidazo pyrimidine derivatives (Scheme-3) catalyzed by starch functionalized magnetite nanoparticles in the aqueous medium at room temperature. Broad substrate scope, high atom economy, easy isolation of products and catalyst from the reaction mixture, excellent conversion, shorter period, chemo selectivity, green solvent, and biocatalyst make this protocol an efficient alternative to the previously reported protocols[18].



Scheme-3: Plausible mechanism for *s*-Fe3O4 catalyzed synthesis of imidazo pyrimidine.

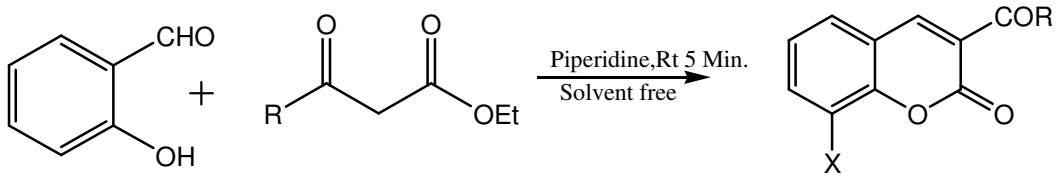
Pagadala et al. (Pagadala et al., 2014) established an ultrasound supported expeditious and straightforward protocol for the one-pot generation of pyridines (Scheme 4) and pyrimidines at room temperature with excellent yields (94– 98%) and (88–95%), respectively.



Scheme -4 : one-pot generation of pyridines derivatives a three component green synthetic route

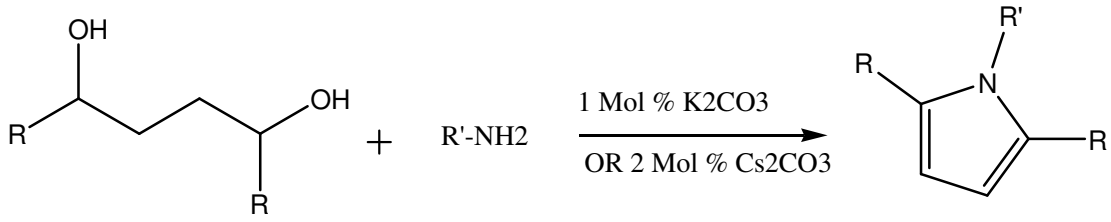
3. Solvent-Free Synthesis: Solvent-free synthesis is a green chemistry approach that eliminates the need for solvents, which are often toxic and hazardous to the environment. This method has been successfully applied to the synthesis of various heterocyclic compounds.

Teizo et. Al. found the Solvent-free Knoevenagel reactions of salicylaldehydes (4)and β-keto esters (2) were also found to proceed efficiently andunder milder reaction conditions than in EtOH solution. 6 Forexample, a mixture of salicylaldehyde (4a, 1.22 g, 10.0 mmol),diethyl malonate (2e, 1.60 g, 10.0 mmol) and a few drops ofpiperidine was mixed and ground well for 5 min at room temperature.[19]



Scheme -5 : Solvent-free Knoevenagel reactions

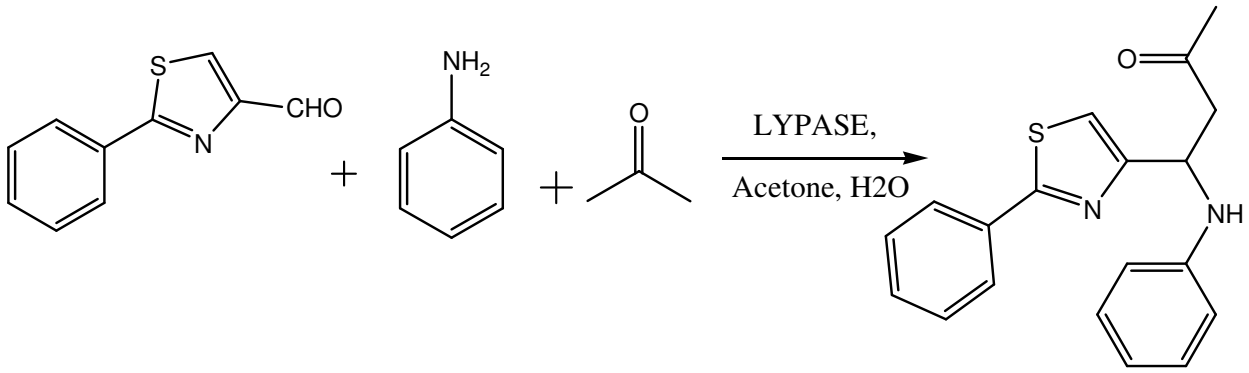
A general, selective, and atom economic metal-catalyzed conversion of primary diols and amines to highly valuable 2,5-unsubstituted pyrroles is catalyzed by a stable manganese complex in the absence of organic solvents. Water and molecular hydrogen are the only side products. The reaction shows unprecedented selectivity, avoiding the formation of pyrrolidines, cyclic imides, and lactones.[20]



Scheme -6 : Preparation of 2,5-unsubstituted pyrroles

4. Biocatalytic Synthesis: Biocatalytic synthesis is a sustainable method that uses enzymes or microorganisms to catalyze chemical reactions. This method offers several advantages, including high regio- and stereoselectivity, mild reaction conditions, and reduced waste generation.

First, various lipases have been evaluated as biocatalysts for the direct Mannich condensation between thiazolic aldehydes, aniline and acetone, in aqueous media (Table 1). Kun Liet al. previously demonstrated that the presence of water in the reaction media strongly influence the activity of lipases in the Mannich type condensation [21]



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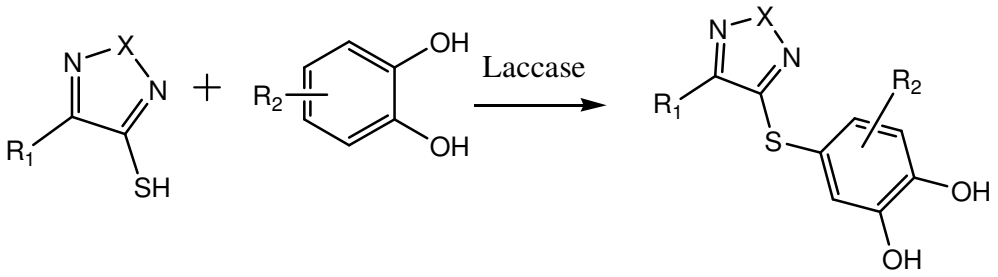
Scheme -7 : Lipase screening for the three-com ponent Mannich type condensation

Donya et. Al. A novel approach for the synthesis of 1,3,4-oxa(thia)diazole aryl thioethers through a biocatalytic strategy has been introduced. By leveraging *Myceliophthora thermophila* laccase (Novozym 51003) as a catalyst, catechol undergoes oxidation to ortho-quinone, facilitating subsequent 1,4-thia-Michael addition reactions. The method offers efficiency and mild reaction conditions, demonstrating promise for sustainable synthesis pathways in organic chemistry. [22]



Scheme -8 : synthesis of 1,3,4-oxa(thia)diazole aryl thioethers through a biocatalytic strategy

Applications of Heterocyclic Compounds:

1. Pharmaceuticals: Heterocyclic compounds are widely used in pharmaceuticals due to their unique biological properties. They are used in the treatment of various diseases, including cancer, HIV, and Alzheimer's disease.

2. Agrochemicals: Heterocyclic compounds are also used in agrochemicals due to their insecticidal, fungicidal, and herbicidal properties.

3. Materials Science: Heterocyclic compounds are used in materials science due to their unique optical, electrical, and magnetic properties.

Conclusion:

The development of eco-friendly methods for the synthesis of heterocyclic compounds is an important area of research that has gained significant attention in recent years. This review article highlights the advantages and limitations of various green chemistry approaches, including microwave-assisted synthesis, ultrasound-assisted synthesis, solvent-free synthesis, and biocatalytic synthesis. Furthermore, we discuss the applications of these heterocyclic compounds in various fields, such as pharmaceuticals, agrochemicals, and materials science. As we move forward, it is essential to continue developing sustainable and environmentally benign methods for the synthesis of heterocyclic compounds.

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