

GREEN CHEMISTRY APPROACHES IN THE SYNTHESIS OF PYRIMIDINE DERIVATIVES

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ABSTRACT

Pyrimidine, a six-membered heteroaromatic molecule, is a structural element found in several essential biomolecules, such as thiamine and nucleosides. Its significant biological activity is important in chemical and medicinal chemistry. Traditional methods for synthesizing pyrimidines often use hazardous solvents and toxic reagents, which can pose a risk to human health and the environment. However, many green chemistry methods have been developed in recent years. These methods use safer and more sustainable techniques, such as catalysts, multicomponent reactions, microwave-assisted synthesis, solventless approaches, mechanical procedures, ultrasonic synthesis, and ionic liquids. These methods produce pyrimidines with higher yields, less environmental impact, and financial gains. They also reduce waste and byproduct generation, shorten reaction times, and simplify workup methods.

Keywords: Pyrimidine, Green Chemistry, Microwave-Assisted, Ultrasound, Multicomponent Reaction.

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INTRODUCTION

A six-membered heterocyclic aromatic pyrimidine has two nitrogen atoms at positions one and three. In nature, essential biomolecules like thiamine, alloxan, and the nucleosides cytosine, thymine, and uracil have the pyrimidine core as a structural component.¹ Due to their great biological activity, pyrimidines are vital in chemical and pharmaceutical chemistry. Critically important therapeutic classes like anti-angiogenesis, anti-diabetic, anticonvulsant, anti-inflammatory, anti-microbial, antithyroid, anti-tubercular, antioxidant, immunomodulators, anti-Alzheimer's, anti-Parkinson's, anti-viral, antiprotozoal, etc., possess pyrimidine nucleus. Pyrimidines also play a role in supramolecular and polymer chemistry. Likewise, the compounds that include pyrimidine nuclei with prolonged conjugation have potential use in molecular wires, light-emitting devices, and ligands with various metals.² Traditional methods for synthesizing pyrimidines often use hazardous solvents and toxic reagents, produce a large amount of waste, require high energy, and negatively impact the environment. To address these issues several green chemistry approaches can be used which act as a unified framework for the design of safer chemical substances and chemical processes to minimize risk at each stage by minimizing waste, maximizing atom efficiency, developing less hazardous chemical synthesis methods, creating safer chemical designs, using safer solvents and additives, optimizing energy efficiency in the design process, incorporating renewable feedstocks, reducing the use of unnecessary derivatives, using catalytic agents, designing for degradation, preventing pollution, and preventing accidents.³ A number of green chemistry methods like catalysis, multicomponent reactions, microwave-assisted synthesis, solventless synthesis, mechanical procedures, ultrasonic synthesis, use of ionic liquids and solventless synthesis can be employed in the synthesis of pyrimidines to overcome the negative impacts of the traditional synthetic methods.⁴

GREEN SYNTHESIS OF PYRIMIDINE DERIVATIVES

Catalytic Approach

Using porous poly-melamine-formaldehyde, Khaligh NG *et al.* created a new catalytic technique for effectively creating novel triazolopyrimidines (mPMF). The procedure was carried out using the planetary ball milling technique following the green chemistry principles. With no loss in catalytic efficiency, the heterogenous catalyst can be employed for up to five further runs. Under environmentally friendly circumstances, many substituted triazolopyrimidines were produced in high yield. This research showed

that POPs (highly porous bifunctional porous organic polymers) with basic spots and acceptor-donor binding groups for hydrogen might be crucial in promoting one-pot multicomponent solid-phase reactions. The primary advantages of this approach are its rapid response time, extensive range of applicable substances, reliance on a metal-free heterogeneous organocatalyst, and simple post-reaction handling.⁵

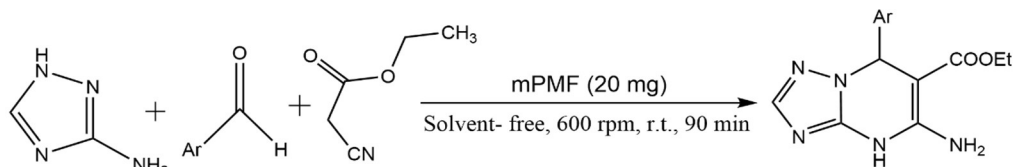


Fig.-1: Synthesis of Substituted Triazolopyrimidines Under Optimized Reaction Conditions

Multicomponent Approach

A novel method for condensing various salicylaldehyde and secondary amines with malononitrile in the presence of $\text{TiO}_2\text{-SiO}_2$ catalyst at 80°C under solvent-free conditions was established by Kabeer SA et.al. It is a cost-effective and environmentally friendly method for synthesizing benzopyrano[2,3-d]pyrimidine derivatives.⁶

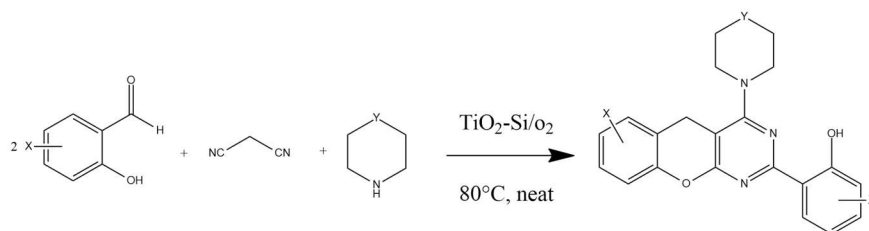


Fig.-2: Synthesis of benzopyrano[2,3-d]pyrimidine Derivatives

Microwave-Assisted Approach

The manufacture of pyrimidine derivatives using environmentally friendly technologies was stressed by Sahoo BM et al. Under basic conditions, condensation of chalcones with urea utilizing microwave heating as an alternative energy source results in a sequence of pyrimidine derivatives. Using Claisen-Schmidt condensation, chalcones were created.⁷

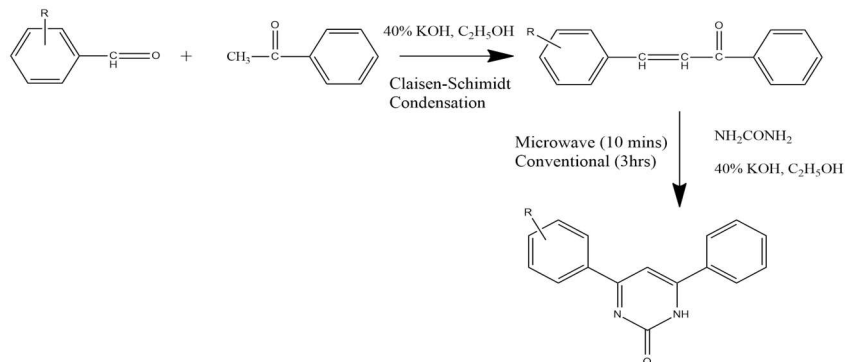


Fig.-3: Synthesis of Phenyl Pyrimidines

Solventless Approach

Sonawane RP *et al.* used the "Grindstone Chemistry Technique," catalyzed by $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ and Conc. HCl, to synthesize dihydropyrimidinones in good yields without the use of solvents. Urea/thiourea, aldehyde derivatives, and 1,3-dicarbonyl compounds are all involved in a multi-component process that gives the DHPM derivative, which uses HCl/ NH_4Cl as a catalyst.⁸

Mechanical Approach

Raj T *et al.* performed a method where modified ZnO NPs were prepared by a sol-gel route using an aromatic capping agent to give a highly efficient catalyst, NS-5, used in the one-pot multicomponent

synthesis of several pyrimidine derivatives through a solvent-free ball milling technique. NS-5 was found to be capable of recycling five times without loss of catalytic nature.⁹

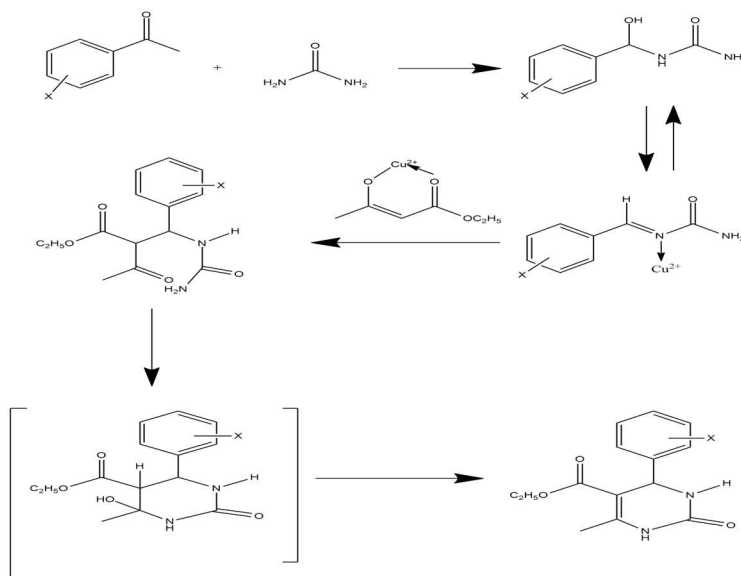


Fig.-4: Synthesis of Various Phenyl Dihydropyrimidines

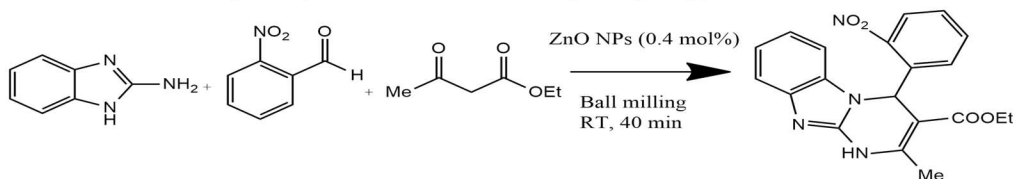


Fig.-5: Synthesis of ethyl 2-methyl-4-(2-nitrophenyl)-1,4-dihydropyrimido[1,2-a]benzimidazole-3-Carboxylate

Ultrasound Approach

Kerru N *et al.* studied the one-pot synthesis benzo[4,5]thiazolo[3,2-a]pyrimidine analogs of pyrimidine using 2-amino-benzothiazole, activated methylene compounds, selected aldehydes, ammonium acetate as a catalyst, and ethanol as a solvent under ultrasound irradiation. This method is considered highly effective and environmentally friendly.¹⁰

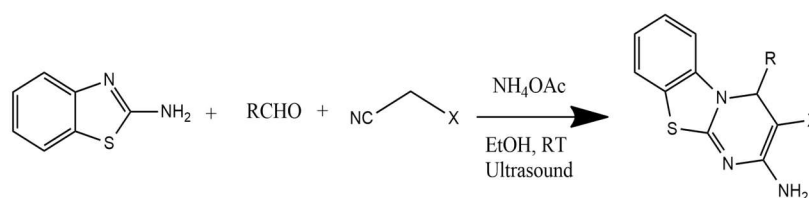


Fig.-6: Synthesis of benzo[4,5]thiazolo[3,2-a]pyrimidine Derivatives

Ionic Liquids

Pyrimidine-2-amine and quinazoline derivatives were produced from cyclic ketones, aldehydes, and guanidine carbonate using several acidic ionic liquids like [DBSO₃HDM]2H₂SO₄, [BSO₃HMIM]HSO₄, and [BSO₃HMIM]CF₃SO₃ heated at 120°C for 10 mins using the microwave to yield 82%, 80%, and 85% of the desired product respectively.¹¹

Organic Synthesis in Water

A straightforward technique for producing benzimidazolopyrimidines and triazolopyrimidine derivatives was described by Liu J, *et al.* by refluxing amino-benzimidazole or amino-triazole, aldehyde, and β-dicarbonyl molecule using a 5 mol% of thiamine hydrochloride (VB1) in a water bath. The catalyst tolerated a range of functional groups, including hydroxyl, methoxy, methyl, chloro, and cyano groups,

demonstrating great activity and producing the desired products. Additionally, acetylacetone was employed as the substrate, and it was discovered that the reaction could proceed without difficulty and produce the products in high yields.¹²

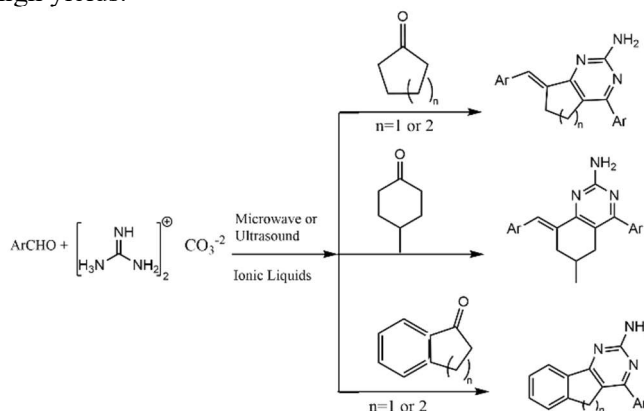


Fig.-7: Synthesis of quinazoline- and pyrimidine-2-amine Derivatives with Cyclic Ketones, Guanidine Carbonate, and Different Aldehydes

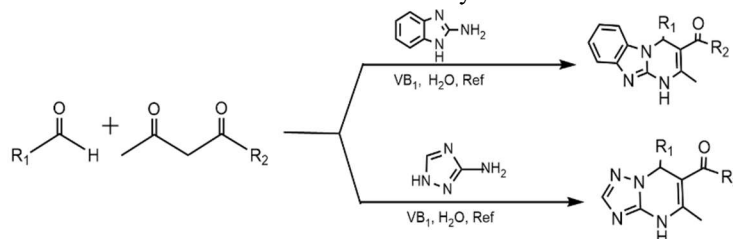


Fig.-8: Synthesis of Benzimidazopyrimidines and Triazolopyrimidines

CONCLUSION

Green Chemistry is considered one of the superior alternatives to conventional synthetic methods due to its financial feasibility, eco-friendliness, high yield, faster reaction rates, minimal toxicity, etc. Several greener approaches for synthesizing pyrimidines have been discussed and proven to yield high-quality products in high quantities. Designing chemical products and processes using a catalyst, MW-assisted synthesis, and ultrasonication fulfills the main objectives of environmental protection, shorter reaction durations, higher yields, altered selectivities, relatively pure products, simpler workup methods, and financial gain. Multicomponent reactions (MCRs) are synthetic operations that yield a specific product from three or more reactants through a series of elementary reactions in a single pot. In the absence of solvents, chemical synthesis offers clean reactions, good product yields quickly, and simple separation, workup, and purification. A mechanical method called ball milling is frequently used to turn powders into tiny particles. Reactants are physically separated, creating an amorphous mixture of all chemicals and a larger surface area for the reaction to occur. Ionic liquids produced for minimal toxicity and biodegradability in focus are frequently referred to as "Green Solvents". So, these techniques could be used in the future to identify the best medicine molecule based on environmentally friendly principles.

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CONFLICT OF INTERESTS

The writers assert that there are no competing interests present.

AUTHOR CONTRIBUTIONS

Each of the authors made substantial contributions to this manuscript, engaging in the review and editing process and giving their approval to the final version for publication. The authors' research backgrounds can be verified by referring to their respective ORCID identifiers, which are provided below:

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