IJRAR.ORG E-ISSN: 2348-1269, P-ISSN: 2349-5138

INTERNATIONAL JOURNAL OF RESEARCH AND ANALYTICAL REVIEWS (IJRAR) | IJRAR.ORG

An International Open Access, Peer-reviewed, Refereed Journal

A review on Green Synthesis of Condensed Pyrimidine Derivatives

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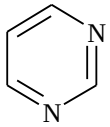
ABSTRACT:

Small and simple heterocyclic structures often have surprising complex biological properties. Many compounds containing this heterocyclic are having pharmaceutical importance. The heterocyclic compound Condensed Pyrimidine and its derivatives are reported to posses varied biological activities .Among the heterocyclic compounds, pyrimidines occupy a central position due to their presence in genetic material of cells. In the present review, a series of methods for the synthesis of pyrimidines . This article aims to review the work reported on the pyrimidine synthesis, the chemistry and the biological activities of pyrimidines.

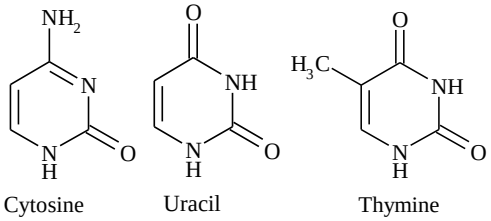
Key words: Green Synthesis, Heterocyclic, Pyrimidines, One pot Synthesis, Derivatives

INTRODUCTION:

Heterocyclic compounds particularly five or six member ring compounds have occupied the first place among various classes of organic compounds for their diverse biological activities. Among the six member ring compounds pyrimidine is the most important six members heterocyclic containing two nitrogen atoms **[1].**



Pyrimidines are present in the three isomeric diazines mainly uracil, thymine, and cytosine.



Cytosine Uracil Thymine

Pyrimidine ring is found in vitamins like folic acid, riboflavin, and thiamine **[2]**, andadd to this, pyrimidine skeleton is also present in synthetic compounds, such as barbituric acid **[3]** and veranal **[4]** which are used as hypnotics **[5]**. Heterocyclic compounds are abundant in nature and are of great significance to life because their structural subunits exist in many natural products such as vitamins, hormones, and antibiotics **[6,7]** Hence, they have attracted considerable attention in the design of biologically active molecules **[8,9]** and advanced organic chemistry **[10,11]**. Also in the family of heterocyclic compounds, nitrogen-containing heterocycles are an important class of compounds in medicinal chemistry and also contributed to society from biological and industrial points which help to understand life processes **[12]**.

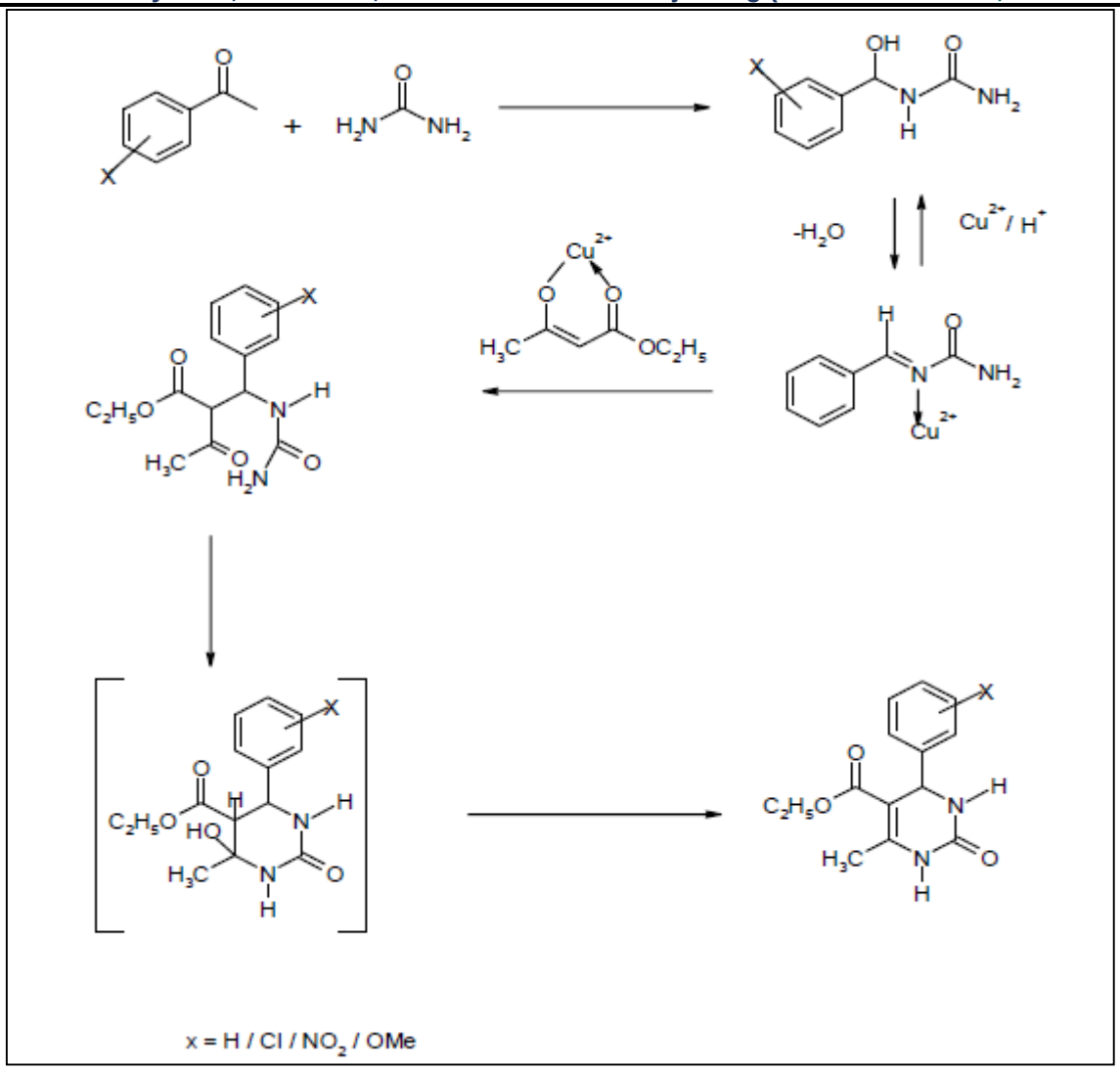
They have a wide range of pharmaceutical and pharmacological applications such as antineoplastic, antiviral, antibacterial, parkinsonism, anthelmintic, vasodilator, antihyperlipidemic, treatment of gastrointestinal roundworms, and disorders associated with hyperuricemia **[13-15].**

Over the year the pyrimidine system turned out to be an important pharmacophore in various marketed drugs such as antineoplastic drugs like Tegafur, Methotrexate, antibacterial drugs like Trimethoprim, Tetroxoprim, antivirals like Idoxuridine, anthelmintic likes Pyrantel Embonate, vasodilators like Dipyridamole, Trapidil, Parkinsonism drug-like Piribedil **[16]**.

Green synthesis of pyrimidine derivatives:

Synthesis of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidine-2-(1H)-one[11]by conventional method and by Grindstone Chemistry.

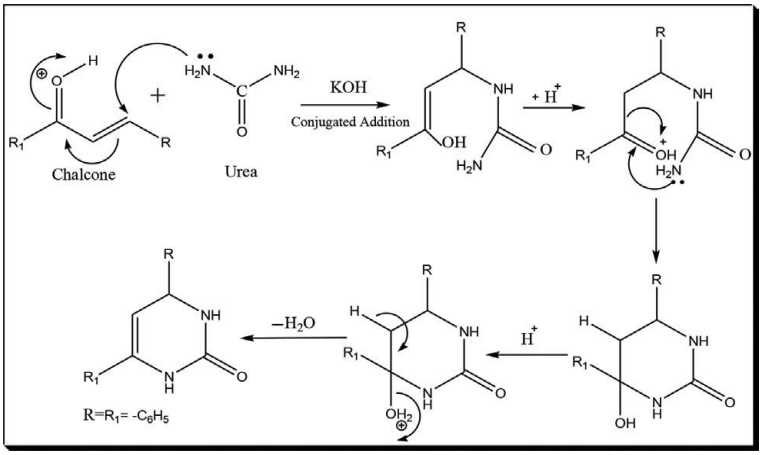
Grindstone Chemistry Technique was catalyzed by $CuCl_2 \cdot 2H_2O$ and Conc. HCl. The obtained products were identified by comparison with spectral data & their melting points. The melting points was obtained 203 °C. The preparation of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidine-2- (1H)-one by Grindstone Chemistry shows synthesis is in good yields and in less time and also avoids problems associated with solvent use. It was found that $CuCl_2 \cdot H_2O$ works as an excellent catalyst for the one-pot three components and solvent free synthesis ofdihydropyrimidione. This technique is superior to the existing methods. [**17]**



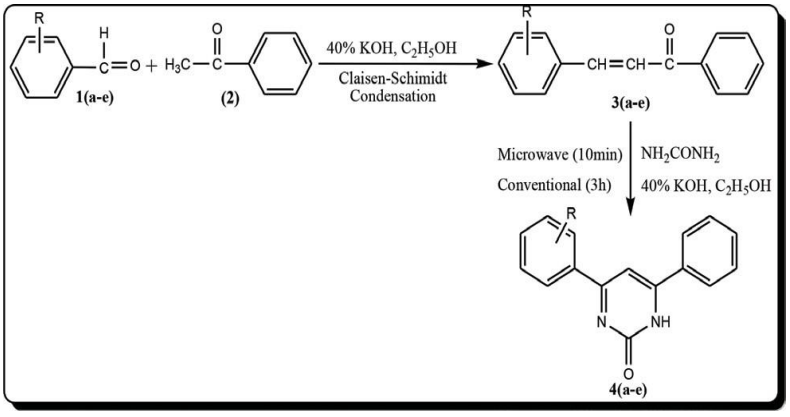
Scheme 1: Synthesis of Synthesis of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidine-2-(1H)-one

Green Expedient Synthesis of Pyrimidine Derivatives via Chalcone:The chalcones were prepared by the Claisen Schmidt condensation of acetophenone **[18]** with various substituted benzaldehyde (1a-e) in the presence of ethanolic potassium hydroxide solution. Both conventional as well as microwave assisted methods followed to prepare a series of pyrimidine derivatives via chalcones by the treatment of chalcones with urea in basic media (Scheme 2).

The prepared compounds along with their reaction time period and percentage yields. By the help of microwave synthesis, the yield of product was increased from 58% upto 85% as compared to conventional synthesis which signifies the utility of green chemistry approach**.[19]**



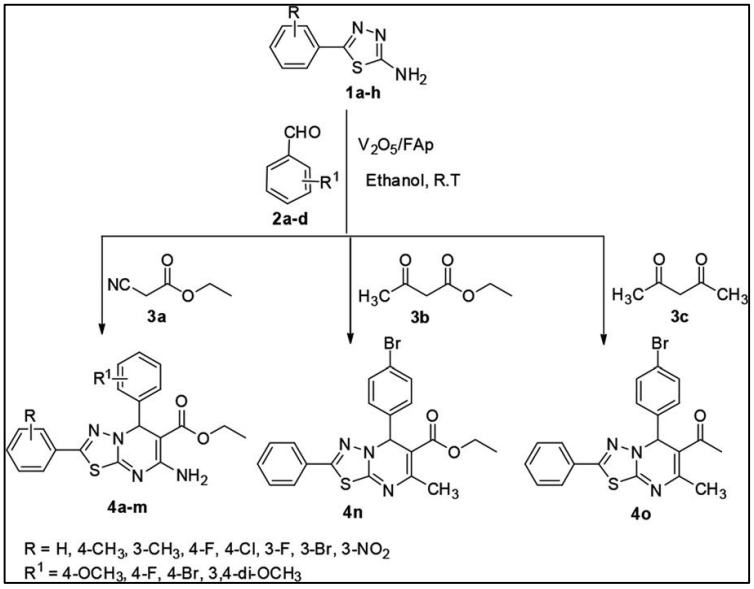
Reaction mechanism involved in formation of pyrimidine via chalcone



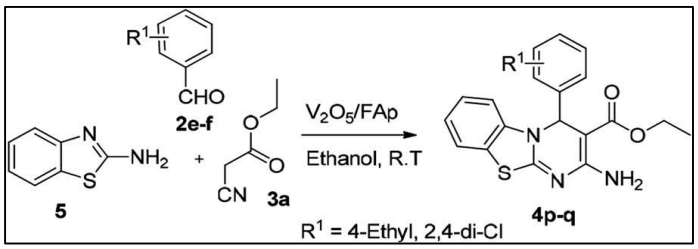
Scheme 2: Synthesis of Pyrimidine Derivativesvia Chalcone

Green synthesis of novel [1,3,4]thiadiazolo/benzo[4,5]thiazolo[3,2-*a*] pyrimidines *via* multicomponent reaction.

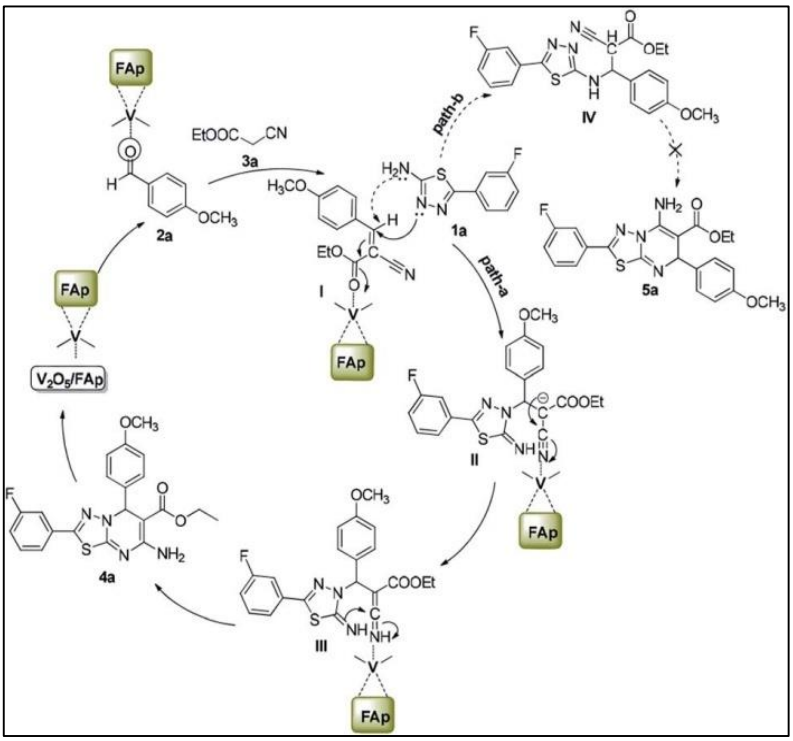
Using vanadium oxide loaded on fluorapatite as a robust and sustainable catalyst Using V_2O_5/FAp as a catalyst, Reported a highly efficient one- pot protocol for the synthesis of seventeen novel [1,3,4]thia-diazolo[3,2-*a*]pyrimidine and benzo[4,5]thiazolo[3,2-*a*]pyrimi-dine analogues. The synergy between the strong acidic properties of vanadia and the amphoteric nature of 2.5% V_2O_5/ FAp composite exhibited superior catalytic activity in ethanol medium at R.T. offering excellent yield (90–97%) of the target products in 25–30 min. the V_2O_5/FAp promoted reaction offers high yields of products at room temperature in shorter reaction time. **[20]**



Scheme 3: Multicomponent synthetic route for novel [1,3,4]thiadia-zolo[3,2-*a*]pyrimidines.



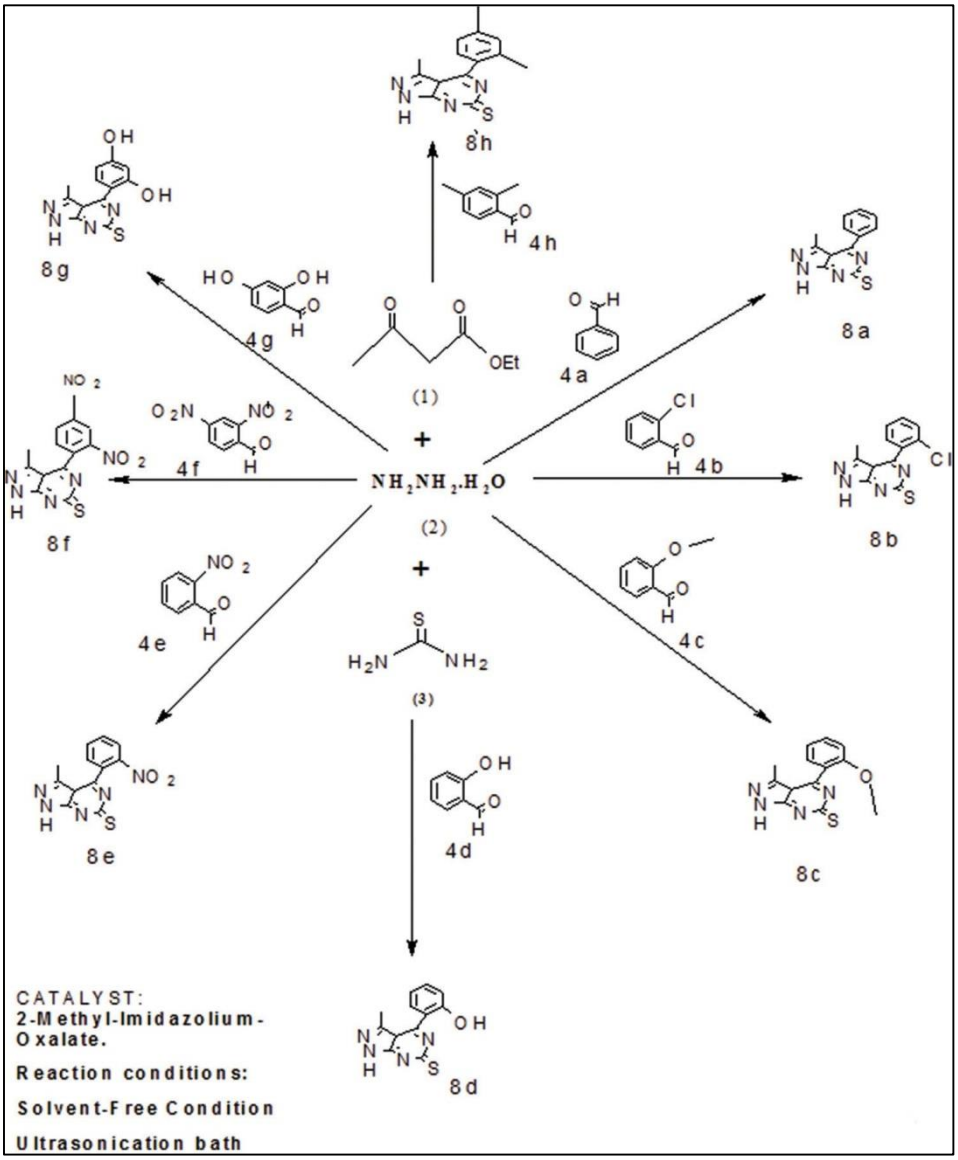
Scheme 4: Multicomponent synthetic route for novel benzo[4,5]thiazolo[3,2-*a*] pyrimidines



Scheme 5: The probable reaction mechanism for the formation of [1,3,4]thiadiazolo[3,2-*a*]pyrimidines

Green synthesis of pyrazolo [3,4]-pyrimidine-thiones using ionic liquid 2-methyl-imidazolium-oxalate

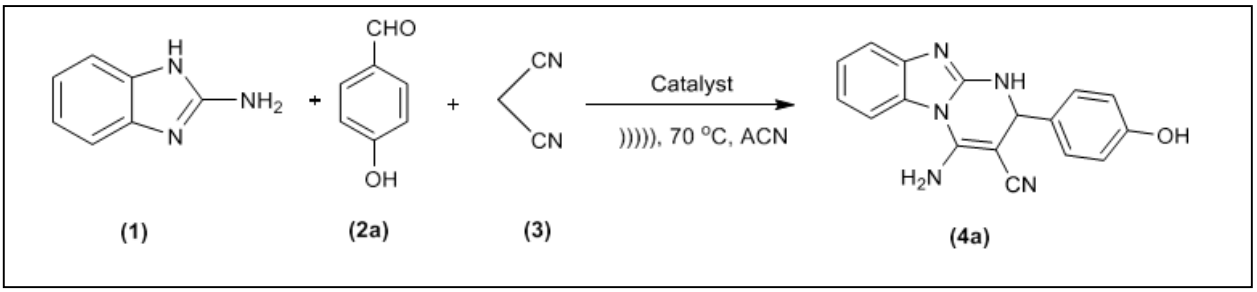
The solvent-free synthesis of pyrazolo [3,4-*d*]-pyrimidine-thiones through ethyl acetoacetate, hydrazine hydrate, thiourea, and different benzaldehydes. An ionic liquid 2-methyl-imidazolium-oxalate catalyzed the reactions under ultrasonication bath. Both conventional and ultrasonic methods were employed and comparison studies have been made. It was found that ultrasonic method completed the reaction quicker than the conventional method. Ultrasonication method is a simple method under which all the reactions were completed at faster time (<7 min) compared to the convention method. Among eight molecules, **8a** and **8d** completed the reactions at a faster rate**. [21]**



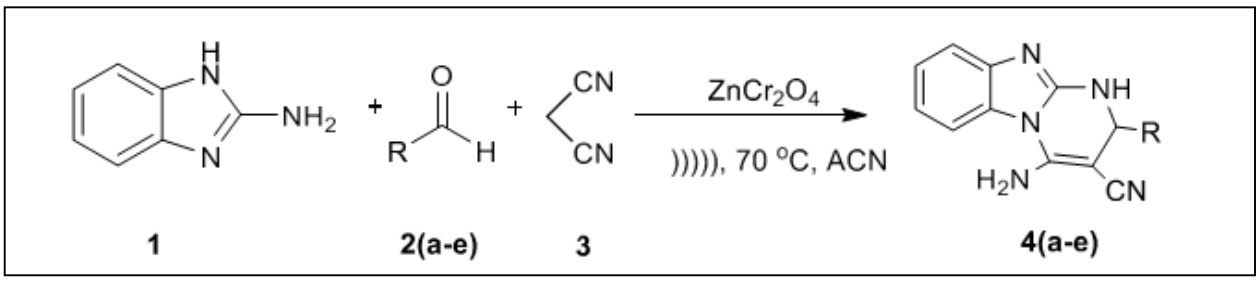
Scheme 6: Schematic representation for the synthesis of pyrazolo-pyrimidine-thiones (8a-8h)

A Facile Synthesis of Pyrimidine Derivatives under Ultrasonic Irradiations by $ZnCr_2O_4$ Nano-Particles Catalyst

The synthesis of 4-amino-2-(R)- 1,2-dihydroxybenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile derivatives (4a-e) from 2- amino benzimidazole **[22]** (1 mmol), substituted aromatic aldehyde (2a-e) (1 mmol), malononitrile (1.5 mmol), using a green catalyst (ZnCr2O4) in acetonitrile solvent under ultrasonic irradiation. The discovered method provides various advantages such as excellent yield,saved reaction time,easy handling,high reaction rate,one-time addition ofther reactant, and a high percentage of yields.**[23]**



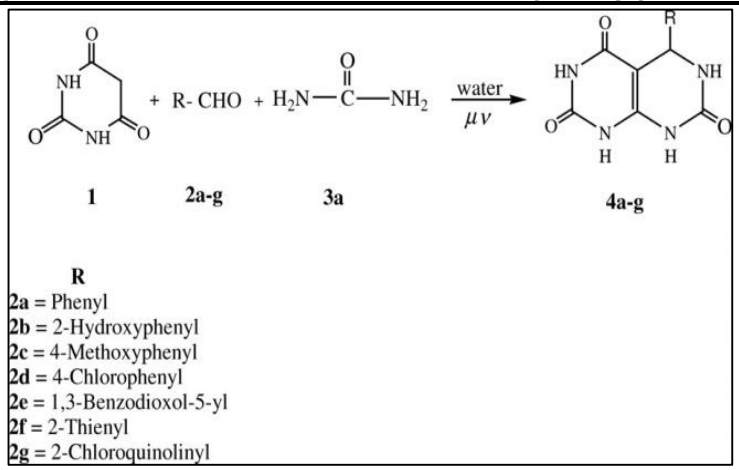
Scheme 7:. Model reaction for screening of synthesis of substituted pyrimidine



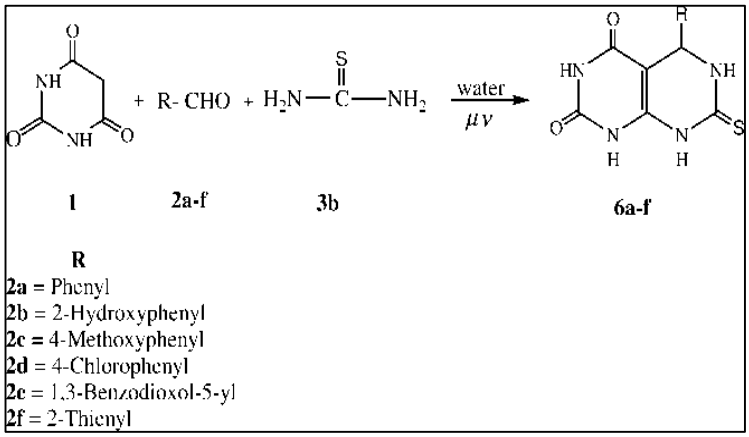
Scheme 8: Synthesis of substituted pyrimidine derivatives(4ae) using heterogenous $ZnCr_2O_4$ under ultrasonic irradiation in acetonitrile solvents

One-pot Green Synthesis for Pyrimido[4,5-*d*]pyrimidine Derivatives

Choosing an appropriate solvent was of crucial importance for the successful microwave-assisted synthesis. To search for the optimal solvent, the reaction of bar- bituric acid (BA, **1**) , aromatic aldehydes **2a** – **g** and urea (**3a**) was examined using water, glycol, DMF, THF or ethanol as solvents under MW irradiation conditions. Some of the reactions were also performed at different powers of microwaves. The reaction proceeded efficiently when water was used as solvent resulting in higher yields in comparison to the other solvents used. Inspired by this result, water was then used as solvent for all further MW-assisted reactions. To optimize the reaction temperature, the synthesis of **4f** was performed in water at temperatures ranging from 70 to 130 ˚C **[24]**



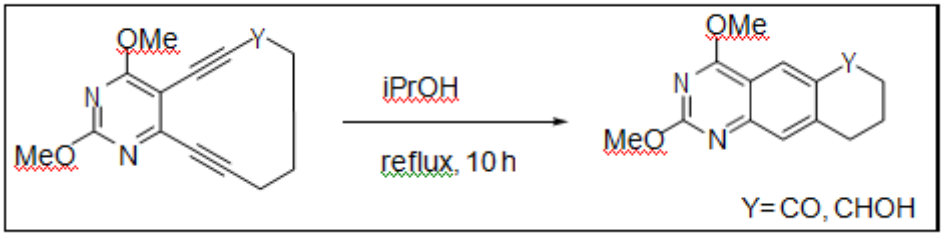
Scheme 9.: One-pot synthesis of pyrimido[4,5-*d*]pyrimidine-triones



Scheme 10.: Synthesis of 7-thioxo-pyrimido[4,5-*d*]pyrimid- ine-diones

Synthesized via a direct oxidative one-pot, three-component reaction:

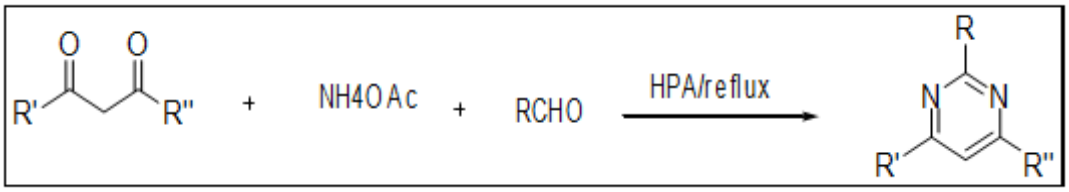
Pyrimidines are synthesized via a direct oxidative one-pot, three-component, reaction between 1,3- diketone, benzaldehydes, and ammonium acetate in the presence of catalytic amounts Keggin-type heteropolyacids under reflux in good yields **[25]**



Scheme 11: Synthesis of pyrimidine derivatives.

Synthesis of various polysubstituted pyrimidines:

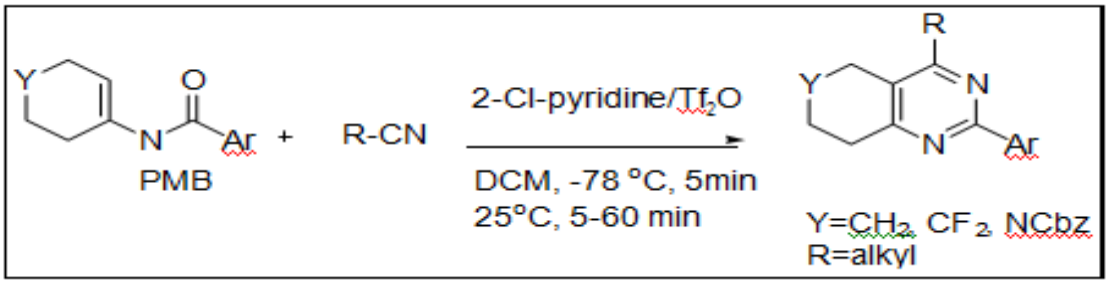
Synthesis of various polysubstituted pyrimidines from in situ generated α,β-unsaturated imines and the corresponding amidine or guanidine derivatives in a convenient one-pot procedure has been reported**[26]**



Scheme 12: Synthesis of pyrimidine derivatives

Synthesis of pyrimidines using β-enaminones:

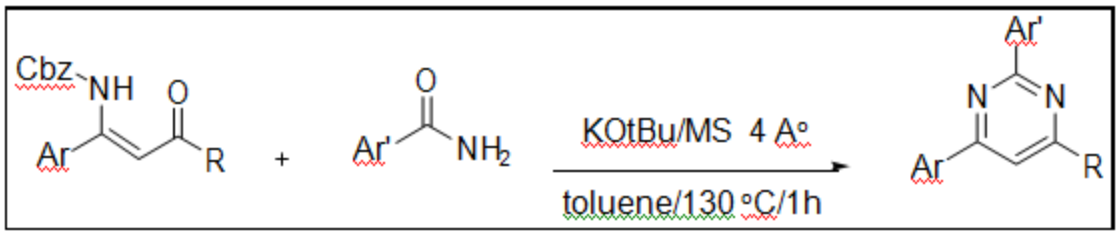
Synthesis of pyrimidines using β-enaminones. was done by Gayon et al (2012). In this procedure propargylic hydroxylamines were rearranged to Cbz-protected β-enaminones on reaction with NaOH in acetonitrile at 50ºC for about 1h. Subsequent synthesis of pyrimidines was achieved from β-enaminones on reaction with corresponding amides in presence of potassium *tert*-butoxide. **[27]**



Scheme 13: Synthesis of pyrimidine derivatives

Synthesis of pyrimidine-5-carbaldehydes from α-formylaroylketene dithioacetals:

Synthesis of pyrimidine-5-carbaldehydes from α-formylaroylketene dithioacetals was reported by Mathews and Asokan (2007). Amidines were allowed to react with α-formylaroylketene dithioacetals in DMF or acetonitrile to obtain the pyrimidine-5-carbaldehydes.**[28]**



Scheme 14: Synthesis of pyrimidine derivatives

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