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A Quick View on Methods of Synthesis of Pyrimidines

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ABSTRACT

Pyrimidine is a five membered heterocyclic ring which is a lead compound for designing potent bioactive agents. This heterocyclic moiety has versatile medicinal significance and has diverse biological activities such as antimicrobial, anticancer, antibacterial, antiprotozoal, antimicrobial, antiviral, antihypertensive, antihistaminic; CNS-active to metabolic adjuvants and many more thus Pyrimidines occupy a distinct and unique place in our life. The present work emphasizes on the various techniques and methods involved in synthesis of various pyrimidine moieties

KEYWORDS

Pyrimidine, Biginelli reaction, condensation

INTRODUCTION[1,2]

Diverse biological and pharmacological properties and actions make heterocyclic compounds analogues and their derivatives an attractive tool for medicinal chemists and researchers. Heterocyles nucleus is present as a core structural component in an array of drug categories such as antimicrobial, anti-inflammatory, analgesic, antiepileptic, antiviral, antineoplastic, antihypertensive and many other complicated and dreaded disorders.

Pyrimidines have a long and distinguished history extending from the days of their discovery as important constituents of nucleic acids to their current use in the chemotherapy of AIDS and other complications. Form deabetogenic agent (Alloxan) to nucleic acid base pairs (Uracil, thymine and cytosine) and in anticancer agents, Antivirals and anti-AIDS, Antitubercular drugs, diuretics, and drugs acting on CNS and in Antifungals, pyrimidine has been in integral ring structure present.[1]

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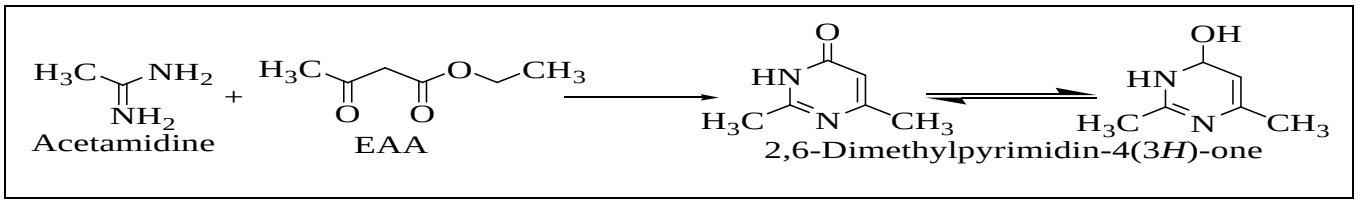
Pyrimidine is a six membered heterocyclic ring having two nitrogen (N) atoms in their ring having molecular formula of $C_4H_4N_2$ and molecular weight = 80 dalton. Pyrimidine is a colourless compound, having melting point 22.5^0C and boiling point 124^0 C. Although an enormous amount of work has been done with pyrimidine derivatives, most of which have been obtained directly from the excellent syntheses available, the chemical reactions of pyrimidine itself been investigated only recently. This is partly because pyrimidine was not readily available, but it can now be obtained quite easily by the decarboxylation of pyrimidine-4, 6-dicarboxylic acid or by the catalytic dechlorination of 2,4-dichloropyrimidine.[2]

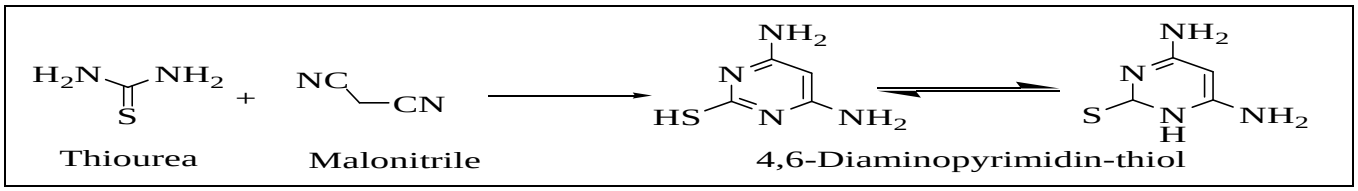
The present review attempts to give a brief account of the Chemistry of Pyrimidine and general Method of Synthesis of Pyrimidine Ring.

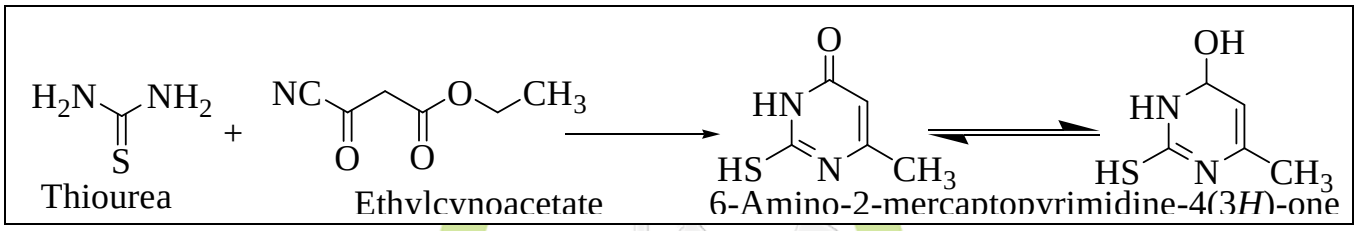
VARIOUS METHODS OF SYNTHESIS OF PYRIMIDINE DERIVATIVES:

1. From C-C-C and N-C-N unit condensation[3]

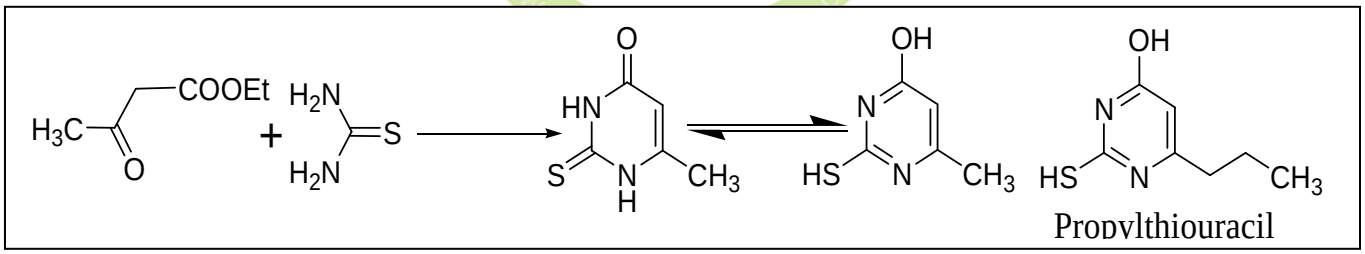
A very important general method for preparing pyrimidine is the condensation between the carbon of the type YCH_2Z, where Y and Z is equal to COR, COOR, CN and compounds havening amidine, urea, guanidine, thiourea and their derivatives. Condensation is carried out in presence of sodium hydroxide or sodium ethoxide.



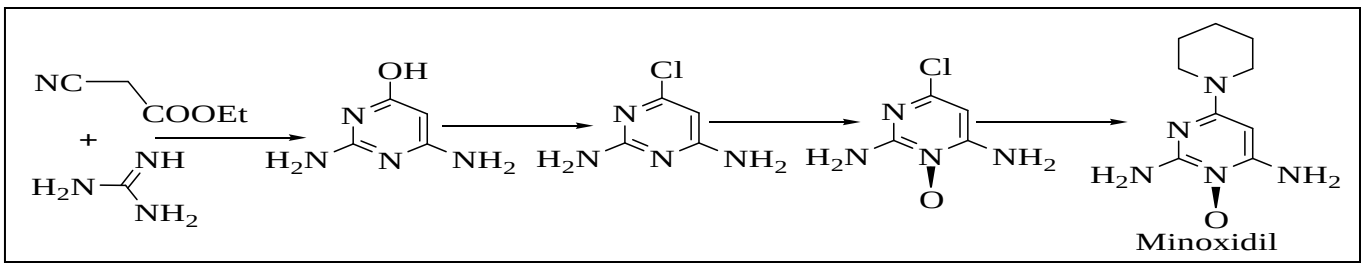




Antithyroid activity was first found in pyrimidine series. The simplest compound to show this activity, methylthiouracil is prepared quite simply by condensation of ethyl acetoacetate with thiourea. Further work in this series shows that better activity was obtained by incorporating of liphophilic side chain. Example: propylthiouracil[4].

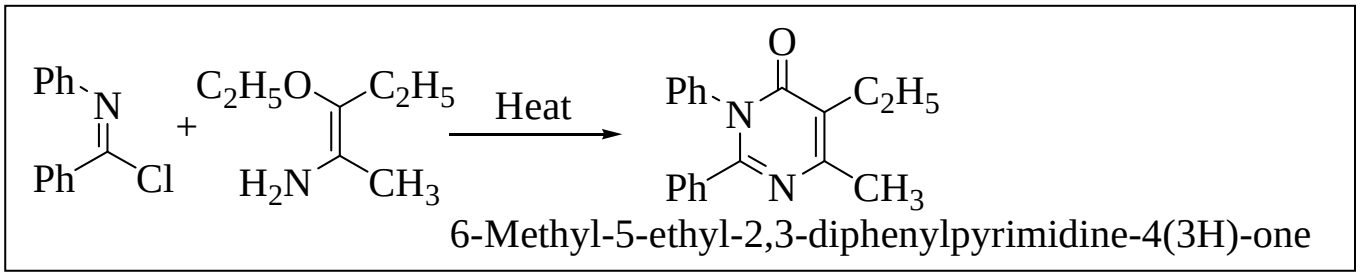


Condensation of ethylcyanoacetate with guanidine in the presence of sodium ethoxide affords the starting pyrimidine. Reaction with phosphorus oxychloride then serves to replace the hydroxyl group by chlorine. Treatment of this intermediate with metachloroperbenzoic acid results in specific oxidation of the nitrogen at the first position Displacement of the halogen with piperidine affords formation of minoxidil[5]. This drug, minoxidil is an extremely effective hypertensive agent acting by means of vasodilatation.



2. from condensation of C-N and C-C-C-N units[3]

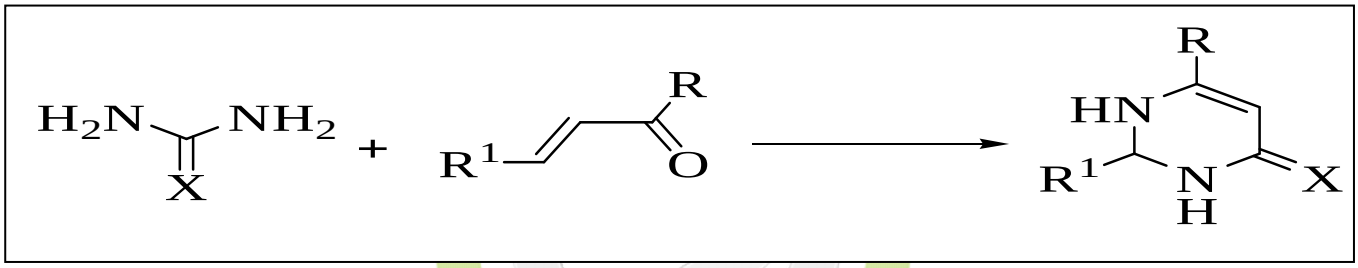
One of the important pyrimidine synthesis involve the condensation between a molecule containing the C-C-C-N unit and a molecule containing C-N unit, e.g. *N*-Phenylbenzene carboximidonyl chloride, isocynotomethane with (C-C-C-N) unit and e.g. 1-ethoxyprop-1-en-2-amine, 3-ethoxypent-2-en-2-amine.



6-Methyl-5-ethyl-2,3-diphenylpyrimidine-4(3H)-one

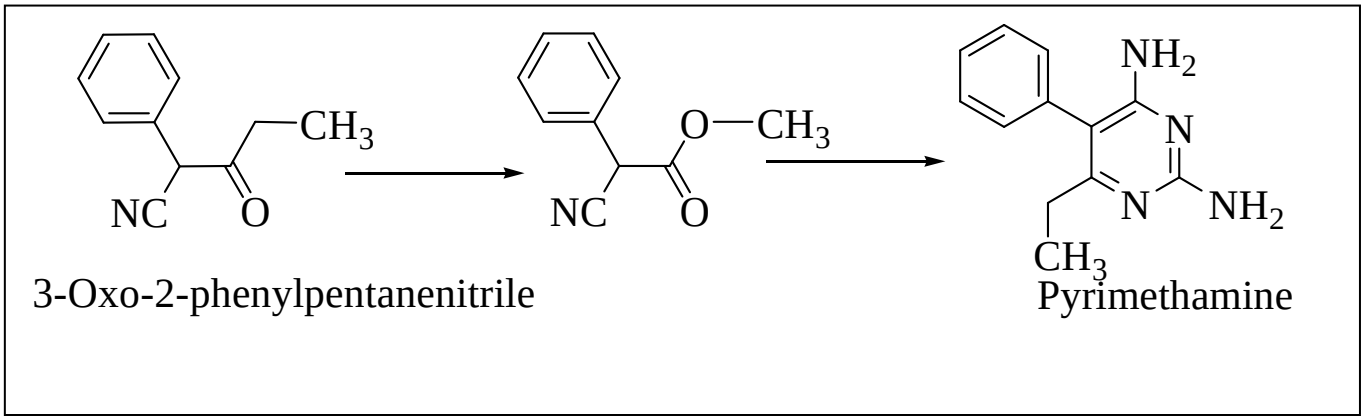
3. From substituted chalcones[6]

Substituted chalcones are treated with urea or thiourea to get substituted thio/oxo- pymidines respectively. These substituted pyrimidines screened for many biological activities.



4. Condensation of phenylacetonitrile with ethyl propionate[7]

2,4-Diaminopyrimidines inhibit the growth of microorganisms by interfering with their utilization of folic acid which lead to an intensive search for anti-infective agents in this class of heterocyclic compounds. This work led to the development of at least two successful antimalarial agents. Condensation of phenylacetonitrile with ethyl propionate in the presence of sodium etoxide gives the cyanoketone treatment with diazomethane affords the methyl enol ether which undergoes condensation with guanidine affords pyrimethamine formation.

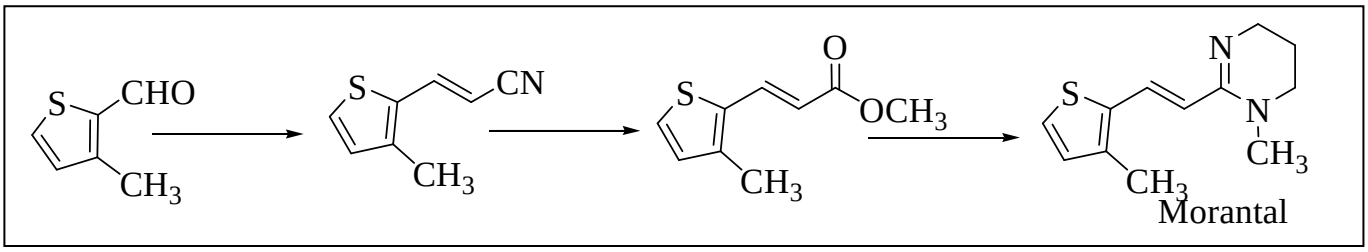


3-Oxo-2-phenylpentanenitrile

Pyrimethamine

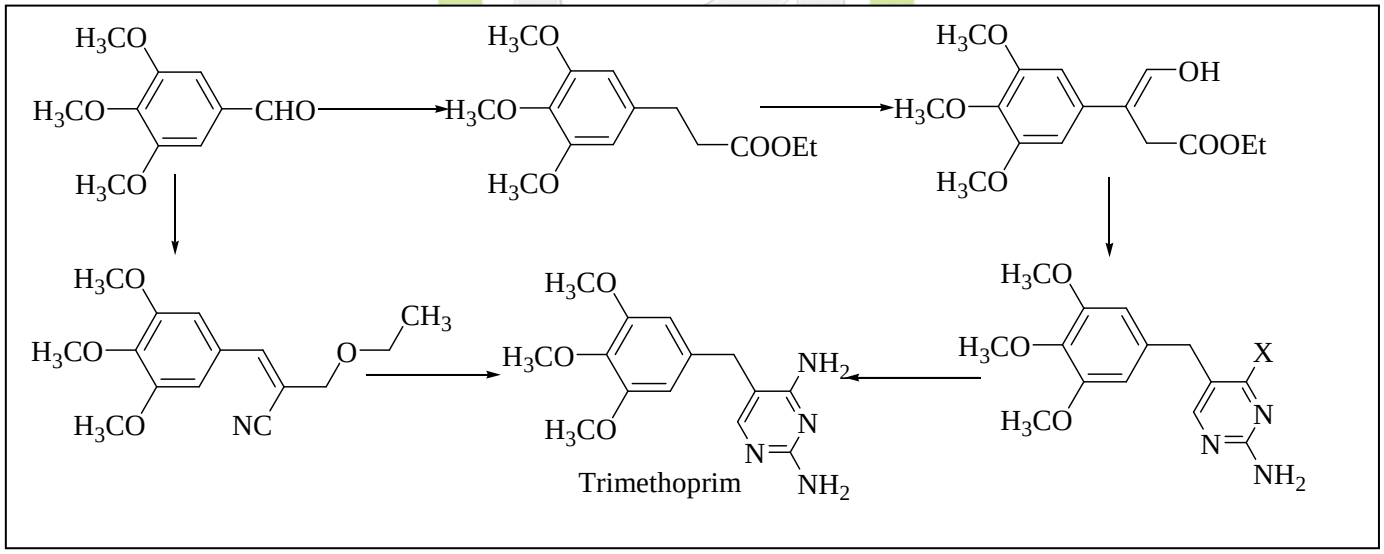
5. From imino-ethers[8]

Knoevenagel type of condensation involves thiophene-2-carbaldehde with cyanoacetic acid gives the corresponding unsaturated nitrile. This is then methylated in the presence of strong acid to afford the imino-ether, condensation with N-methyl propolene 1, 3-diamino proceeds probably by addition-elimination of each amino group in turn with the iminoether. There is thus pyrantal. The analog, morantal is obtained by the sequence using 3-methylthiophene-2-carboxaldehde.



6. From malonic ester synthesis[9]

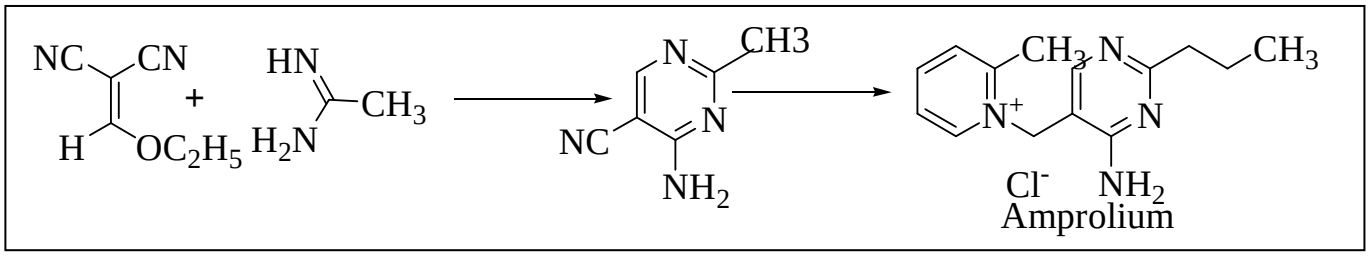
Bis-homologation of benzaldehyde (for example, reduction of aldehyde to alcohol, alcohol to halide and then to malonic ester), affords the hydocinnamic acid. Formation with ethyl formate and base gives the hydroymethylene derivative. The hydroxyl group is then converted to amine by successive treatment with phosphorus oxychloride and ammonia. There is thus obtained the antimalarial agent, Trimethoprim.



7. Condensation of ethoxymethylene malonitrile with acetamidines[10]

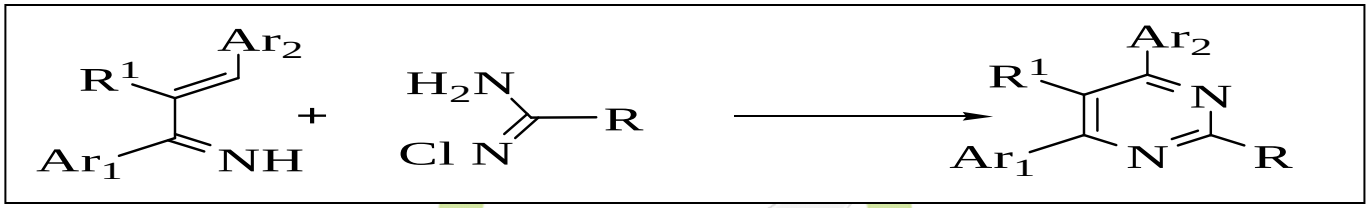
Coccidia are protozoans that can wreak havoc in a flock of poultry the infection known as coccidiosis. Agents that control this disease coccidiostats are in view of the world's heavy dependence on poultry as a source of protein, of great economic significance. One of the more important drugs for treatment of this disease incorporates the pyrimidine nucleus. Condensation of ethoxymethylene malononitrile with acetamidne affords the substituted pyrimidine. This reaction involves conjugate

addition of the amidine nitrogen to the malononitrile followed by loss of ethoxide, addition of remaining amidine nitrogen to one of the nitrile will then lead to the pyrimidine. Reduction of the nitrile gives the corresponding amino methyl compound exhaustive of the amine followed by displacement of the activated quaternary by bromide ion affords the key intermediate, displacement of the halogen by α-picoline gives amprolium.



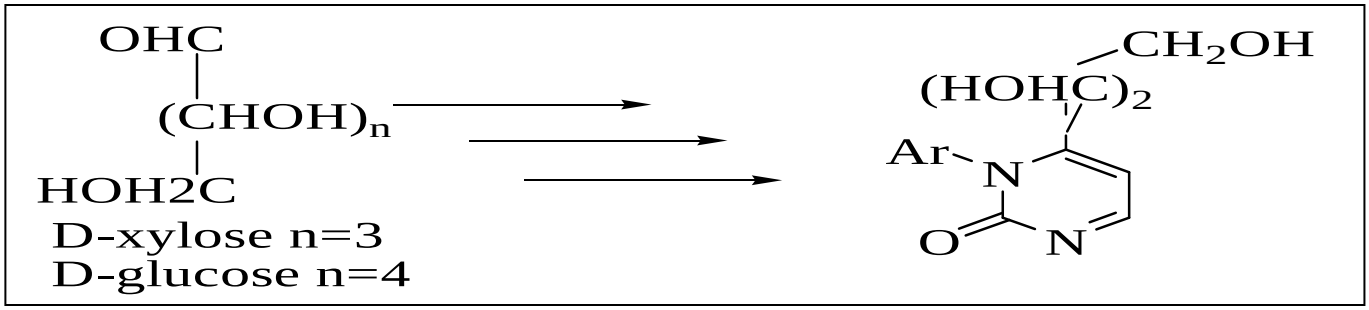
8. From α,β-unsaturated imines[11]

A series of polysubstituted pyrimidines were synthesized from in situ generated α,β-unsaturated imines and the corresponding amidine or guanidine derivatives in a convenient one-pot procedure.



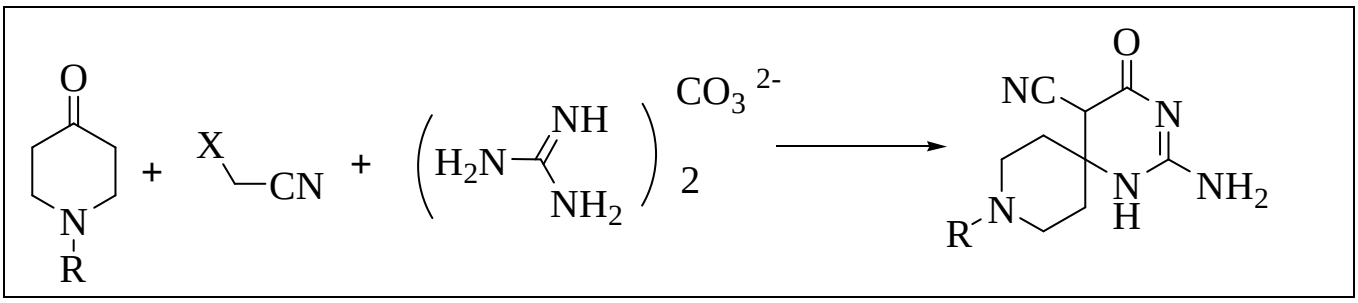
9. From Aza-Michael addition[12]

A novel and expeditious synthetic protocol for functionalized pyrimidine using unprotected aldoses as bio renewable resources is reported. The synthesis involves Aza-Michael addition of aromatic amines to aldose-derived 1,3-oxazin-2-ones (thiones) followed by dehydrate ring transformation to afford 4-polyhydroxyalkylpyrimidin-2-ones (thiones). This is a one-pot Montmorillonite K-10 clay-catalyzed amine-driven process proceeding under solvent-free microwave irradiation conditions.



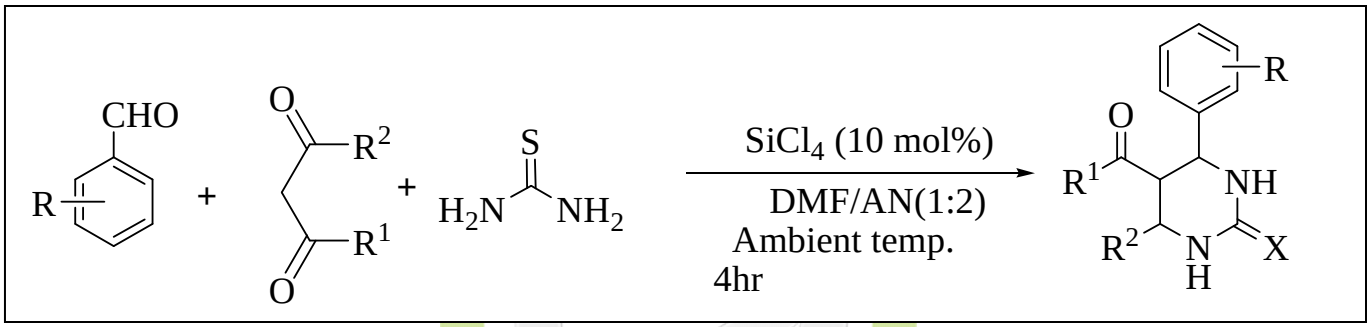
10. From three-component condensation[13]

A novel and efficient protocol is developed for the synthesis of various spiro-2-amino pyrimidines via the three-component condensation of alkyl cyanoacetates, Guanidinium carbonate and N-substituted 4-piperidinones in ethanol at reflux. High yields, neutral conditions and short reaction times are advantages of this method.



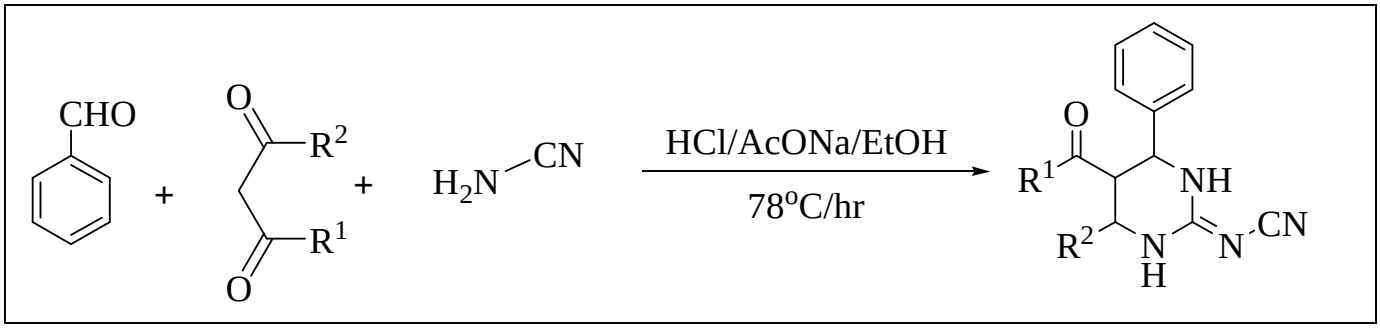
11. From Biginelli reaction[14]

Multicomponent one-step fusion of a variety of pharmacologically pertinent pyrimidine heterocycles has efficiently been achieved from their respective aldehydes, β-dicarbonyl compounds and urea/thiourea in the presence of a catalytic amount of tetrachlorosilicane in DMF/AN mixture at normal ambient temperature.



12. From four-component Biginelli-type reaction[15]

4-Aryl-2-cyanoimino-3,4-dihydro-1*H*-pyrimidine derivatives have been prepared using multicomponent reaction by reacting a mixture of arene orheteroarenecarbaldehyde, 1,3-dicarbonyl compounds and cyanamide under acidic conditions. The novelty of this approach derives from its use of cyanamide as a building block in a four-component Biginelli-type reaction. Varying the reaction conditions led to the formation of either N-(2-imino-6-phenyl-1,3,5-oxadiazinan-4-ylidene) cyanamide or 3,4-dihydropyrimidine-2(1*H*)-one. The type of heterocycle skeleton synthesized depends on the nature of the acid catalyst as well as the reaction conditions employed.



CONCLUSION

Pyrimidine nucleus is one of the most important heterocycle exhibiting remarkable pharmacological activities. Involvement of pyrimidine in several biological reactions make it an attractive target for research community and may be helpful in discovery of new drugs for several incurable ailments.

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