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Synthesis and Biological Activities of Pyrimidines: A Review

Ramchander Merugu*, Swetha Garimella, Deepthi Balla and Kalyani Sambaru

University College of Science and Informatics, Mahatma Gandhi University, Nalgonda

Abstract: 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 have been reported along with some biological activities of pyrimidines. This article aims to review the work reported on the pyrimidine synthesis, the chemistry and the biological activities of pyrimidines.
Key words: Pyrimidines, synthesis, biological activity.

Introduction

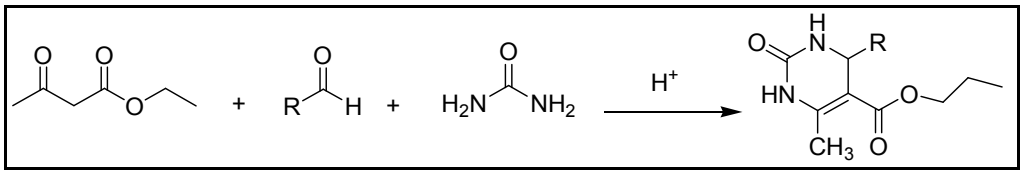
The chemistry of heterocyclic compounds is important for the discovery of novel drugs. Various natural compounds such as amino acids, alkaloids, vitamins, hormones, hemoglobin, and many synthetic drugs and dyes contain heterocyclic ring systems. Large numbers of synthetic heterocyclic compounds like pyrimidines, pyrrole, pyrrolidine, furan, thiophene, piperidine, pyridine and thiazole show significant biological activity. Among these pyrimidines are of great interest[1,2]. After Scheele isolated uric acid in 1776, fused pyrimidine chemistry started. Pyrimidine is a six membered heterocyclic ring with two nitrogen (N) atoms in their ring. It is a colorless compound, having molecular formula of C4H4N2 and molecular weight of 80 dalton having melting point 22.5^{o}C and boiling point 124^{o}C. Pyrimidine is a weaker base than pyridine, imidazole or amidines as addition of a proton does not increase the resonance energy like imidazole and amidines. Understanding the metabolism of pyrimidines is important for drug metabolism of pyrimidine derivatives[5]. Only one of the nitrogen atom of the pyrimidine can be alkylated by alkylating agents, but with triethyloxoniumborofluoride both nitrogen atoms can be alkylated. Some of the biologically active pyrimidine derivatives are quinethazone, trimethotrexate, prazosin, , folic acid and riboflavin[6].

Synthesis of Pyrimidines:

Pyrimidines are prepared by condensation reactions between three carbon compounds and compounds with amidine structure in the presence of catalyst sodium hydroxide or sodium ethoxide. eg condensation of acetamidine with ethylacetoacetate to form 4-hydroxy-2, 6-dimethylpyrimidine[7]. $ZnCl_2$-catalyzed three-component coupling reaction for the synthesis of various 4,5-disubstituted pyrimidine derivatives was reported by Sasada et al[4]. Decarboxylation of malic acid with concentrated sulphuric acid produces β-ketoacid which reacts with urea to produce uracil which gives pyrimidine[8]. Reaction of sodium salt of 3,3-dimethoxy-2-methoxycarbonylpropen-1-ol with amidinium salts afforded 2-substituted pyrimidine-5-carboxylic esters[9]. Samarium chloride catalyzed novel and efficient synthesis of pyrimidine from β-formyl enamide by cyclisation of β-formyl enamides using urea under microwave irradiation was reported[10]. Single-step conversion of various N-vinyl and N-aryl amides to the corresponding pyrimidine and quinazoline derivatives was reported[11]. Tetra substituted saturated fused pyrimidines has been synthesized through a simple and efficient one-pot operation[12]. Most common method for pyrimidine synthesis is Biginelli reaction. Condensation of carbonyls with amines forms the basis for most other methods. Reaction of certain amides with carbonitriles under electrophilic

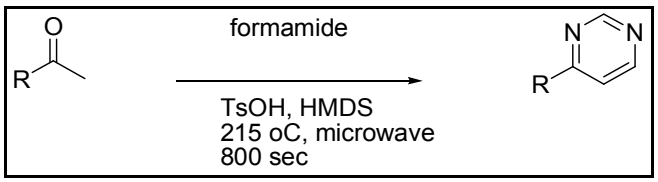
activation of the amide with 2-chloro-pyridine and trifluoromethanesulfonic anhydride also results in the formation of pyrimidine. The position 5 of pyrimidine is the most susceptible to electrophilic attack. In the presence of activating groups, electrophilic substitution occurs, but only at position 5. Nucleophilic reagents such as sodamide and phenyl magnesium bromide attack positions 2, 4, and 6 of pyrimidine. Numerous synthetic modes of pyrimidines have been reported starting from thiobarbituric acid[13] (TBA), chalcones[14] and thioureas[15] and they are found to have medicinal properties[16,17]. Most widely used technique for pyrimidine synthesis is that of Biginelli reaction (**Scheme 1)**

Scheme 1:



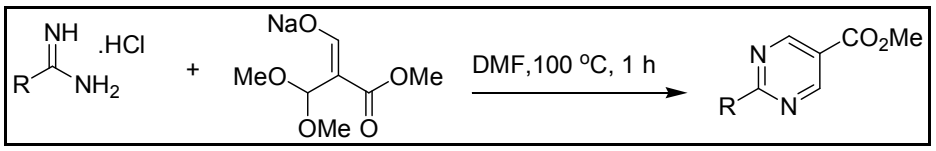
A simple, high yielding synthesis of pyrimidines from ketones in the presence of HMDS and formamide is reported Under microwave irradiation[18].

Scheme 2:



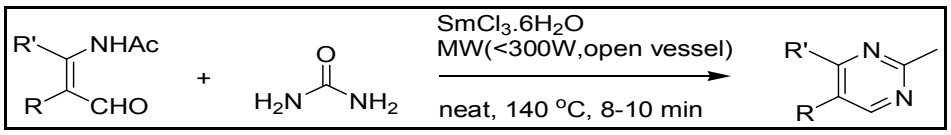
A method for the synthesis of 2-substituted pyrimidine-5-carboxylic esters is described in this approach. The sodium salt of 3,3-dimethoxy-2-methoxycarbonylpropen-1-ol has been found to react with a variety of amidinium salts to afford the corresponding substituted pyrimidines esters[19].

Scheme 3:



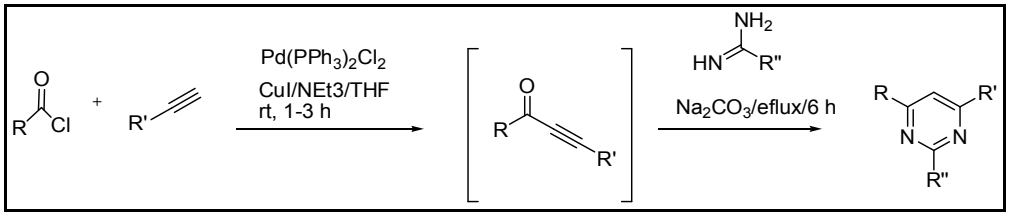
A novel and efficient synthesis of pyrimidine from β-formyl enamide involves samarium chloride catalyzed cyclisation of β-formyl enamides using urea as source of ammonia under microwave irradiation was also reported[20].

Scheme 4:



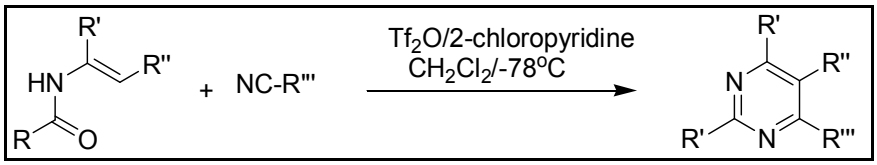
The coupling of acid chlorides with terminal alkynes using one equivalent of triethylamine under Sonogashira conditions followed by subsequent addition of amines or amidinium salts to the intermediate alkynones allows a straightforward access to enaminones and pyrimidines[21].

Scheme 5:



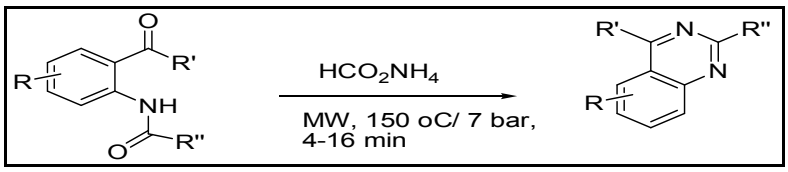
A single-step conversion of various *N*-vinyl and *N*-aryl amides to the corresponding pyrimidine and quinazoline derivatives involving amide activation with 2-chloropyridine and trifluoromethanesulfonic anhydride followed by nitrile addition into the reactive intermediate and cycloisomerization to get pyrimidines[22].

Scheme 6:



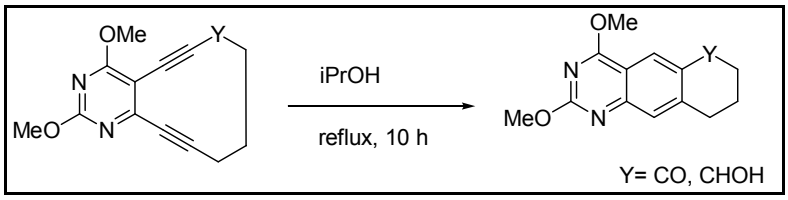
A photo chemically induced Fries rearrangement of anilides gave several *ortho*-aminoacylbenzene derivatives that were acylated. These acylamides underwent rapid microwave-assisted cyclization to 2,4-disubstituted quinazolines (and benzoquinazolines) in the presence of ammonium formate[23].

Scheme 7:



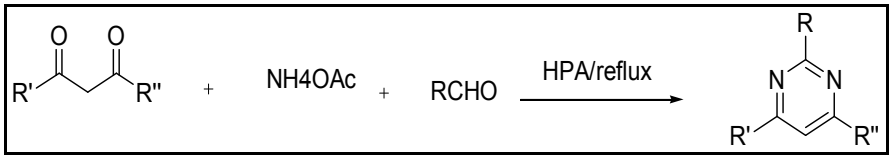
Novel 10-membered pyrimidine enediynes were synthesized in seven and eight steps[24].

Scheme 8:



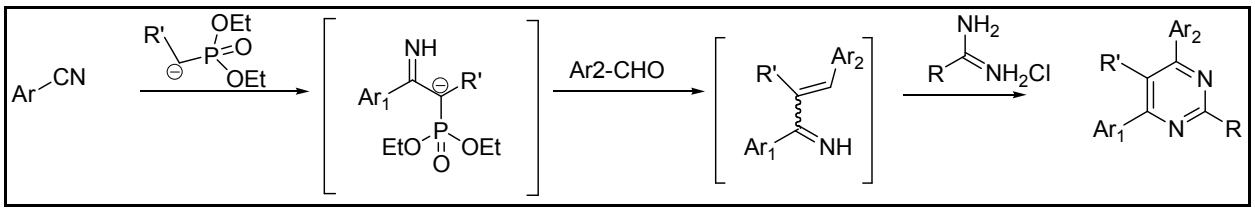
Pyrimidines are synthesized via a direct oxidative one-pot, three-component, reaction between 1,3-diketone, benzaldehydes, and ammonium acetate in the presence of catalytic amounts Keggin-type heteropolyacids under reflux in good yields[25].

Scheme 9:



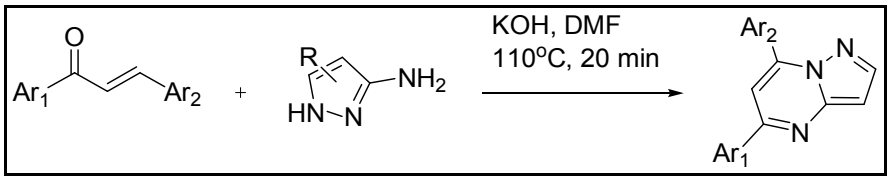
Synthesis of various polysubstituted pyrimidines from in situ generated α,β-unsaturated imines and the corresponding amidine or guanidine derivatives in a convenient one-pot procedure has been reported[26].

Scheme 10:



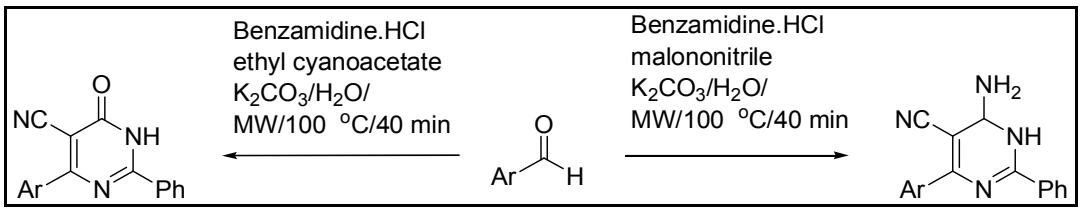
KOH mediated synthesis of pyrimidines through amines and chalcones was also reported by Kaswan et al (2014)[27].

Scheme 11:



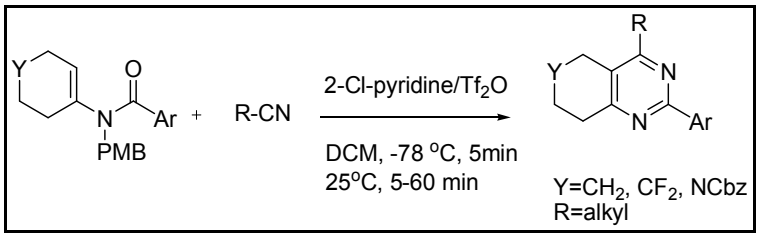
Xavier et al (2013)[28] reported multicomponent microwave assisted synthesis of pyrimidine derivatives.

Scheme 12:



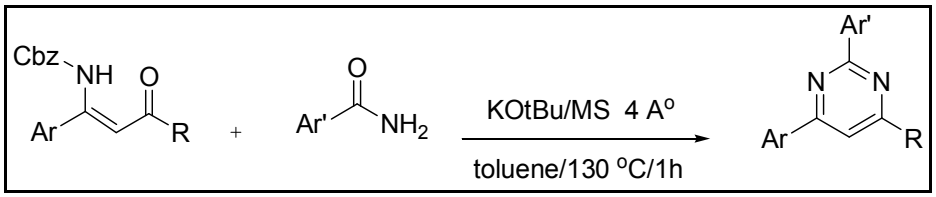
An array of tetrasubstituted saturated fused pyrimidines have been synthesized using N-PMB group for the synthesis of a broad range of *N*-vinyl tertiary enamide starting materials for pyrimidine synthesis[29].

Scheme 13:



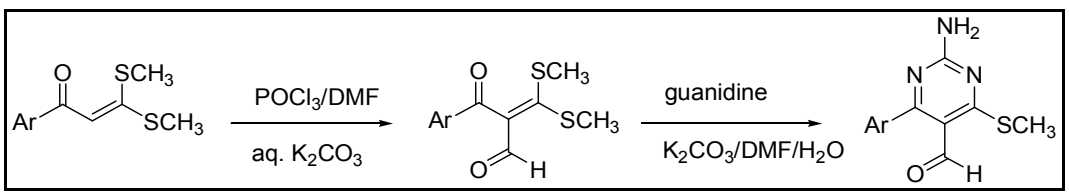
Synthesis of pyrimidines using β-enaminones. was done by Gayon et al (2012)[30]. In this procedure propargylic hydroxylamines were rearranged to Cbz-protected β-enaminones on reaction with NaOH in acetonitrile at 50°C for about 1h. Subsequent synthesis of pyrimidines was achieved from β-enaminones on reaction with corresponding amides in presence of potassium *tert*-butoxide.

Scheme 14:



Synthesis of pyrimidine-5-carbaldehydes from α-formylaroylketene dithioacetals was reported by Mathews and Asokan (2007)[31]. Amidines were allowed to react with α-formylaroylketene dithioacetals in DMF or acetonitrile to obtain the pyrimidine-5-carbaldehydes.

Scheme 15:



Biological Activities

Pyrimidine derivatives are well known for their medicinal properties due to the presence of pyrimidine base in thymine, cytosine and uracil, which form the building blocks of DNA and RNA[32]. These bases are also found in Vitamins[33]. Hypnotics like veranal and alloxan are known for its diabetogenic action contains these bases[34,35]. Antifungal activity against *A. niger, A. flavus, C. falcatum* and *P. infestans*[36,37]. Thieno pyrimidines have been reported to have anti hyper lipidemic activity[38]. Pyrimidine-based antimetabolites structurally related to the endogenous substrates that they antagonize eg antineoplastic activities have been shown by 5-Thiouracil[39]. N-methyl-N-pyrimidin-2-yl glycines, have been synthesized and were found to have anti-inflammatory activity[40]. New scaffold with Pyrimidine having inhibitory activity against HIV-1 integrase were reported[41]. 2-Thiouracil and its analogue, thiobarbital are effective drugs against hyperthyroidism[42]. Some pyrimidines synthesized had significant antihistaminic activity when compared to mepiramine[43]. A novel series of 3-substituted 5H-thiazolo[3,2-a]pyrimidine derivatives as Acetyl choline esterase (AChE) inhibitors have been reported which could bind with the active site of human AChE substrate domain[44]. Antimicrobial activities of pyrimidines have also been reported in our earlier work[45-50].

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