Chapter-3

Biological Importance and Chemistry of Pyrimidine

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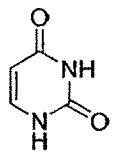
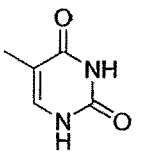
3.1. Biological importance of pyrimidine

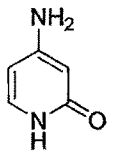
The pyrimidine moiety is one of the most widespread heterocycle in biologically occurring compounds, such as nucleic acids and vitamin B_1, and is an important constituent of numerous drug molecules in many therapeutic areas. Pyrimidines, because of their long history of biological and medicinal significance, occupy unique and important place amongst various heterocycles The use of these omnipresent biomolecules in the chemotherapy against AIDS, cancer, malaria and cardiovascular diseases is now well known The synthesis and biological significance of a variety of pyrimidine derivatives continues to be of interest to the medicinal chemist



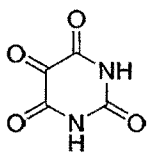
Uracil (**171a**)



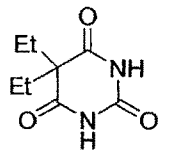
Thymine (**171b**)



Cytosine (**171c**)

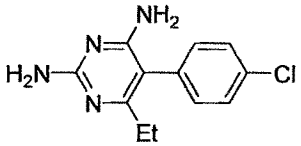


Alloxan (**171d**)

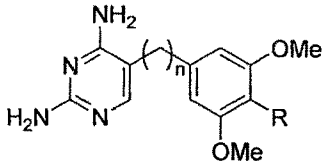


Barbitone (**171e**)

Uracil (**171a**), thymine (**171b**) and cytosine (**171c**) are the three important constituents of the nucleic acids [446-449]. Amongst these uracil and thymine are important constituents for controlling the metabolism, reproduction and growth of living organism, especially, in the transcription of genetic conformation and biosynthesis of proteins Alloxan (**171d**) is known for its diabetogenic action in a number of animals [448] Thus, many important chemotherapeutic agents have been synthesized based on this pyrimidine skeletal Notable amongst the drugs having a pyrimidine nucleus are the barbiturates, which were used in the therapy for a long time for their hypnotic, sedative and anticonvulsant properties. Barbitone (diethyl barbituric acid, **171e**) was the first hypnotic to be introduced in medicine in the year 1903 [450]



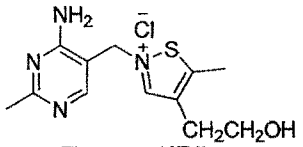
Pyrimethamine (**172**)



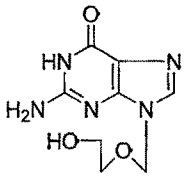
Trimethoprime (**173a**), n = 0, R = OMe
Brodimoprim (**173b**), n = 1, R = Br

The inhibitors of the essential bacterial enzyme DHFR, 2,4-diaminopyrimidines like pyrimethamine (**172**) and trimethoprim (**173a**), find use in the antimalarial therapy

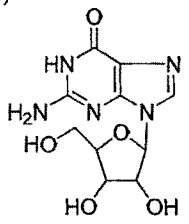
Brodimoprim (**173b**) is another 2,4-diaminopyrimidine that selectively inhibits bacterial DHFRs to a similar or greater extent than trimethoprim [451]



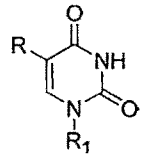
Thiamine (**174**)



Acyclovir (**175a**)

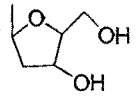


Vidarabine (**175b**)

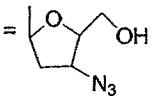


5-Fluorouracil (**176a**) R = F, R_1 = H

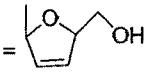
Idoxuridine (**176b**), R = I, R_1 =



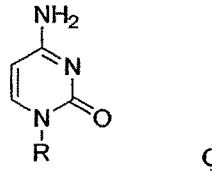
Zidovudine (**176c**), R = Me, R_1 =



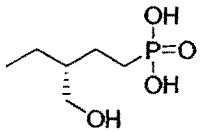
Stavudine (**176d**), R = Me, R_1 =



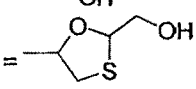
Thiamine (**174**), a pyrimidine derivative, was the first vitamin to be discovered in Vitamin B series [448] Purine [acyclovir (**175a**), vidarbine (**175b**) etc] and pyrimidine [5-fluorouracil (**176a**), idoxuridine (**176b**), zidovudine (AZT, **176c**), stavudine (**176d**) etc] derivatives have been developed as important chemotherapeutic agents and find widespread use in anticancer and antiviral chemotherapy [452] A number of specialized reviews have been published which describe the contribution of these important classes of molecules.[453-460] Retrovir® (AZT, **176c**) is a potent inhibitor of the *in vivo* replication and cytopathic effects of HIV and has been recently approved for use against AIDS and severe AIDS-related complex (ARC).[460]

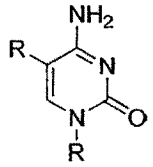


Cidofovir (**177a**), R =

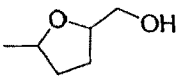


Lamivudine (**177b**); R =





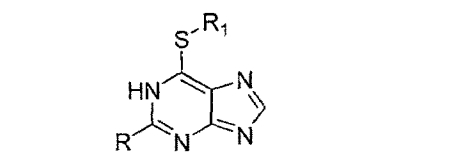
Zalcitabine (**177c**); R = Me, R_1 =



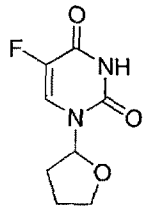
Flucytosine (**177d**); R = F, R_1 = H

Cidofovir (**177a**), an antimetabolite for deoxycytosine triphosphate is used for treatment of cytomegalovirus (CMV) in AIDS patients [459] Lamivudine (**177b**), zalcitabine (**177c**) and stavudine (**176d**) are effective anti-AIDS drugs when used in

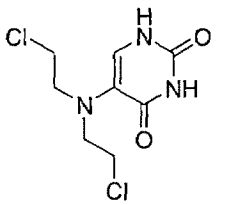
combination with zidovudine.[459,460] Pyrimidines also exhibit antifungal properties Flucytosine (**177d**) is a fluorinated pyrimidine used as nucleosidal antifungal agent for the treatment of serious systemic infections caused by susceptible strains of *Candida* and cryptococcus [461]



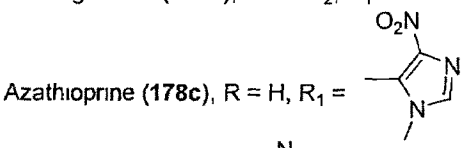
6-Mercaptopurine (**178a**), R = H, R_1 = H
6-Thioguanine (**178b**), R = NH_2, R_1 = H



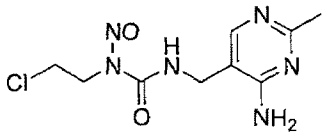
Tegafur (**179**)



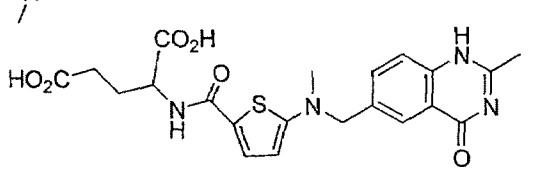
Uramustine (**180**)



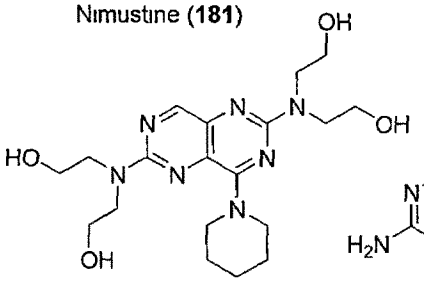
Azathioprine (**178c**), R = H, R_1 =



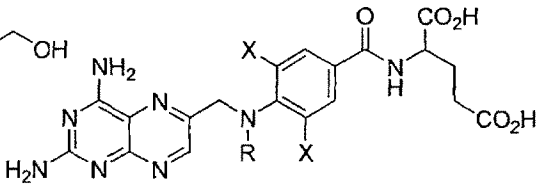
Nimustine (**181**)



Raltitrexed (**182**)



Mopidamol (**183**)

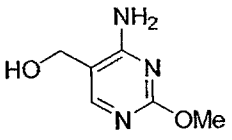


Methotrexate (**184a**), R = Me, X = H
Aminopterine (**184b**), R = X = H

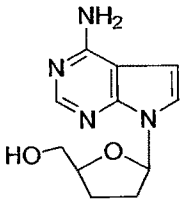
The antineoplastic compounds possessing the guanine nucleus like mercaptopurine (**178a**), thioguanine (**178b**), azathioprine (**178c**), tegafur (**179**), etc were discovered after formulation of the antimetabolite theory by Woods and Fildes in 1940 These drugs prevent the utilization of normal cellular metabolite [450,460] There are many more in recent times, like uramustine[465] (**180**), nimustine[463] (**181**), raltitrexed[464] (**182**) and mopidamol[462] (**183**). The very potent but nonselective DHFR inhibitors methotrexate (**184a**) and aminopterine (**184b**) are important anticancer agents.[466]

Besides this, there are few examples of pyrimidine antibiotics The simplest of all is bacimethrin (**185**), which was isolated in 1961 from *Bacillus megatherium*, is active against several staphylococcal infections *in vivo* and has anticarcinoma activity in mice [467] Antibiotic tubercidin (**186**) is reported to exhibit antitumor activity and its

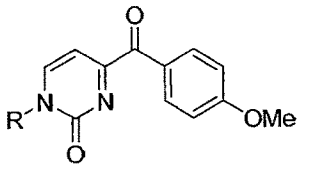
effect on mycobacteria was also investigated.[468] Gougerotin (**187**), a cytosine derivative, is active against mycobacteria as well as, several Gram-positive and Gram-negative bactena [469] There are more derivatives of cytosine, namely amicetin (**188a**) and plicacetin (**188b**), which exhibit activity against acid fast and Gram-positive bacteria as well as some other organisms [468] The anti-TB cyclic peptide antibiotics capreomycin and viomycin also contain pyrimidine nucleus



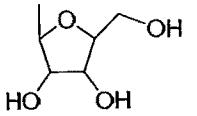
Bacimethrin (**185**)

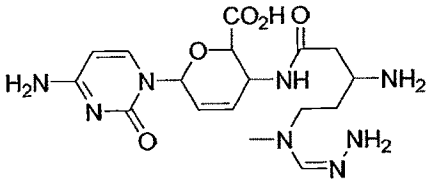


Tubercidin (**186**)

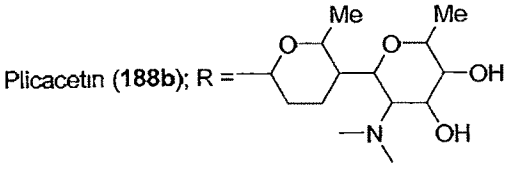


Amicetin (**188a**); R =

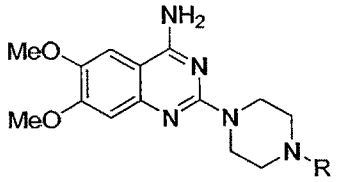


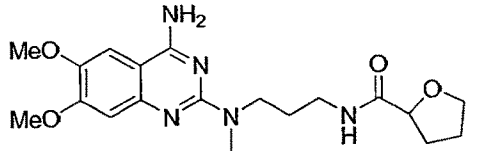


Gourgetin (**187**)



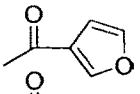
Plicacetin (**188b**); R =



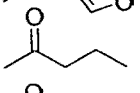


Alfuzocin (**190**)

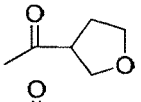
Prazocin (**189a**); R =



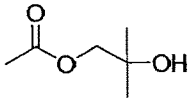
Bunazocin (**189b**); R =

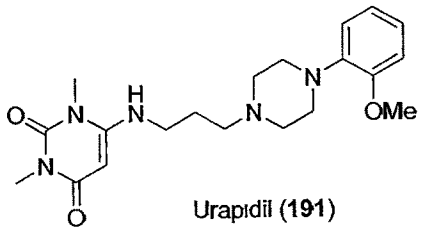


Tetrazocin (**189c**); R =



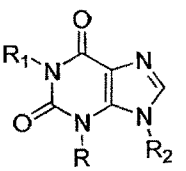
Trimazocin (**189d**); R =

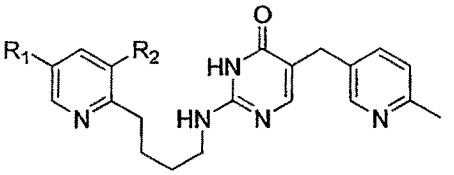




Urapidil (**191**)

Several condensed pynmidine derivatives have shown potent antihypertensive activity Prazocin (**189a**), a quinazoline derivative, is a selective α_1-adrenoceptor antagonist.[470] Its related analogs, bunazocin (**189b**),[471] terazocin (**189c**),[472] and trimazocin (**189d**),[472,473] are also found to be potent antihypertensive agents Alfuzocin (**190**),[474] a prazocin analogue, and urapidil (**191**)[475] are used especially in urinary obstruction caused by benign prostate hyperplasia.

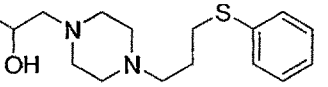




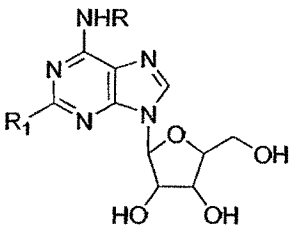
Temelastine (**193a**); R_1 = Br, R_2 = Me
Icotidine (**193b**); R_1 = H, R_2 = OMe

Xanthine (**192a**); R, R_1, R_2 = H
Theophylline (**192b**); R, R_1 = Me, R_2 = H
Proxyphylline (**192b**), R, R_1 = Me, R_2 = $CH_2CH(OH)CH_3$

Tazıphylline (**192b**); R, R_1 = Me, R =



Several xanthine (**192a**) derivatives such as theophylline (**192b**), aminophylline and proxyphylline (**192c**) exhibit good bronchodilator activity.[476] Tazıphylline (**192d**) is ten times more potent than either astemizole or terfenadine in its affinity for H_1-histamine binding site and appears to be devoid of CNS activity [468] Another pyrimidine containing antihistaminic drug, temelastine (**193a**) is comparable to mepyramine.[477] Radiolabelled studies have indicated that it does not penetrate the CNS appreciably Icotidine (**193b**), a structural analogue of temelastine lacks CNS activity and is a dual antagonist of both H_1 and H_2 receptors.[478] Besides their bronchodilatory action, certain xanthine derivatives are used therapeutically as diuretic, cardiac stimulant and vasodilator Especially, pentifylline (**192a**: R_1 = C_6H_{13}, R, R_2 = Me) and pentoxyphilline (**192a**· R_1 = C_4H_9COMe, R, R_2 = Me) are used in cardiovascular disorders



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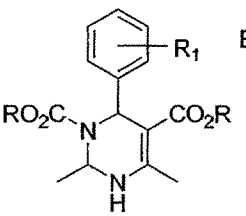
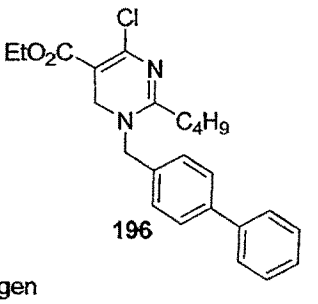


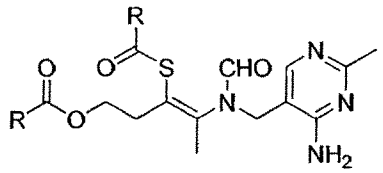
195; R = Me, Et
R_1 = NO_2, halogen



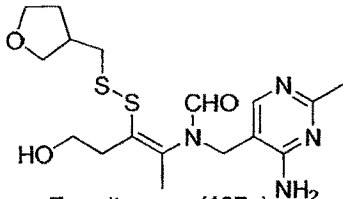
196

The analogues of caffeine and theophylline (**194**) have been found to be relatively selective inhibitors of phosphodiesterase enzymes (PDEs)[479] as well as adenosine A_1- and A_2-receptor antagonist [480] Dihydropyrimidines (**195**) are reported as biologically active molecule and their calcium channel blocker activity with potent and long lasting vasodilatory and antihypertensive activity has been described.[481]

Angiotensin II antagonistic activity has been reported for certain pyrimidines of the type **196** [482]

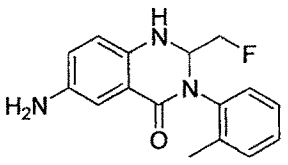


Acetiamine (**197a**); R = Me
Bentiamine (**197b**); R = C_6H_5

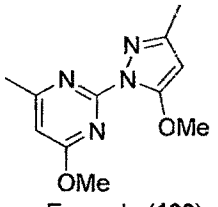


Fursultiamine (**197c**)

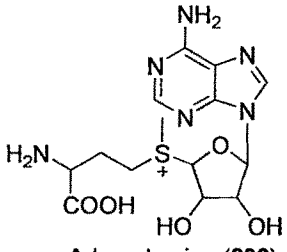
Acetiamine (**197a**), bentiamine (**197b**) and fursultiamine (**197c**) are new lipid-soluble forms of thiamine having therapeutic use in beriberi, polyneuritis, encephalopathy, pain, malnutrition and alcoholism [468] These agents are especially useful in the treatment of long-standing insulin-dependent diabetes mellitus. Fursultamine has been reported to inhibit the arachadonic acid cascade-line activation and reverse the increase in coronary blood flow.



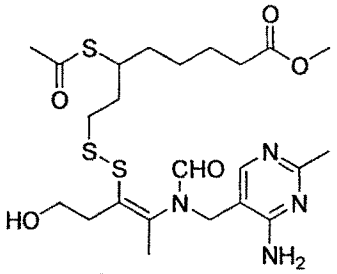
Afloqualone (**198**)



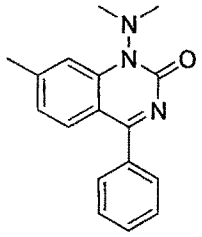
Epirizole (**199**)



Ademetionine (**200**)



Octotiamine (**201**)

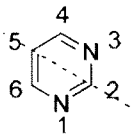


Proquazone (**202**)

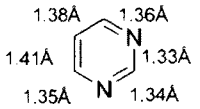
Several non-steroidal antiinflammatory drugs (NSAIDs) are also consisting pyrimidine nucleous [468] Afloqualone (**198**) has been evaluated as a successful anti-inflammatory agent with lower back pain patients Epirazole (**199**) is suggested to be a COX-2 inhibitor Ademetionine (**200**) is primarily used in conjunction to glucosamine and chondroitin therapy Octotiamine (**201**), a vitamin B_1 derivative also exhibits anti-inflammatory activity Proquazone (**202**), a condensed pyrimidin-2-one derivative has been reported to exhibit good NSAID potential

3.2. Chemistry of pyrimidine

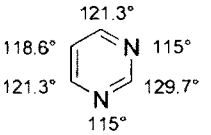
Pyrimidine is the most widely studied diazine containing two N atoms at 1 and 3 positions. The replacement of the two "CH" units which are meta to each other in a benzene ring by two N atoms, generally results in an induced symmetry with bonds of unequal length. However, it retains its symmetry about the 2,5-axis so that three differing pairs of equal bond lengths result.[483]



203a



203b

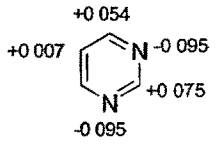


203c

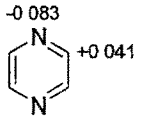
In addition to this, the electronegative N atoms constitute high density centers for the π-electrons which are otherwise equally distributed about the ring system in benzene. Therefore, the reactivities of 2,4-/6- and 5-carbon atoms of pyrimidine as well as, the substituents attached to them, vary individually. The substitution in the pyrimidine ring will also decide the overall symmetry of the pyrimidine ring.

3.2.1. Geometry of pyrimidine

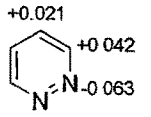
The pyrimidine ring is virtually flat. Electron density at the positions *ortho* and *para* to the electronegative N atoms is more in the pyrimidine than the other two diazines, pyrazine and pyridazine. This is because the two N atoms of the pyrimidine ring are so positioned that their individual effects reinforce each other, and thus act in unison. The resultant effect is greater in the pyrimidine than its isomeric diazines, in which the electronic effect of the two N atoms instead of adding up, in fact, partly antagonize each other. Thus, there is considerable depletion of electron density at the positions 2- and 4/6- in the pyrimidine ring while the position C-5 retains some electronegativity though only to a lesser extent. At the same time, the localization of π-electrons at the two N atoms results in decreased aromaticity of pyrimidine ring. Thus, pyrimidine is not truly aromatic; whatever little resemblance of aromaticity is left in the system is at the C-5 position. This decreased stability of pyrimidine is also reflected in that there is no good correlation established between the theoretical and experimental determination of the resonance energy values for pyrimidine, which have been given as 8, 14, 20, 26, 33, 38 or 40 Kcal/mole, compared with a value of 41 Kcal/mole for benzene. Pyrimidine can be appropriately compared with m-dinitrobenzene, which too has lower resonance energy.[484]



204a



204b



204c

The above electron density distribution diagrams, which shows the gain or loss of π-electrons at each atom of the molecule, has been calculated for all the three isomeric diazines by the refined VESCF method (Variable Electronegativity Self Consistent Field Method) and further substantiate this point This localization of electrons then explains the unique character and basis of pyrimidine chemistry.

3.2.2. Ionization of pyrimidine

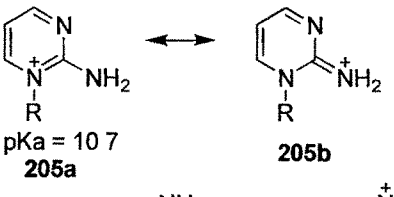
Pyrimidine is a much weaker base (pK_a 1 31) than pyridine (pK_a 5.2) because the second ring N shares the available π-electrons with the first and the system therefore approximates to 3-nitropyridine (pK_a 0 8) Its basicity is intermediate to that of the other two isomeric diazines, pyridazine (pK_a 2.33) and pyrazine (pK_a 0 6) respectively [485] Various substituents and their positions in the pyrimidine ring affect the overall electron density and thus the ionization constant as seen with the insertion of various groups (Table 3 1)

Table 3.1 pK_a values of substituted pyrimidines

Functional groups	pK_a	Functional groups	pK_a
5-NO_2	0 35	2-OH	2.24
5-CN	0.7	2-NH_2	3.54
5-Br	1 95	4-NH_2	5 71
4-CH_3	2 0	5-NH_2	2.8
2,4-di-CH_3	2 8	4,5-di-NH_2	6.03
4,6-di-CH_3	2 8	2,4-di-NH_2	7 3
4-OCH_3	2 5	2,4,5-tri-NH_2	7.63

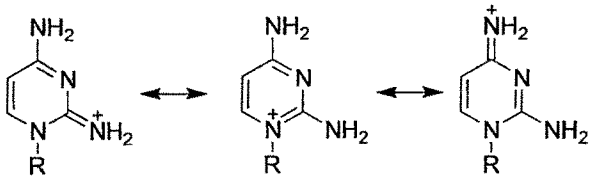
Resonance stabilizes the cations thereby increasing the basic strength Thus, high basicity of 2- and 4-aminopynmidines is due to the increased resonance stabilization of the respective cations. Alkylation of aminopyrimidines on a ring N gives an imine of quite high basic strength (pK_a 10.7) because its cation has typical and effective stabilization (however, the pyrimidinones, pyrimidinethiones, pyrimidinecarbocylic

acids, all ionizes as acids but because pyrimidine is such a weak base, the formation of zwitterionic species seldom occurs).[483]



pKa = 10 7
205a

205b

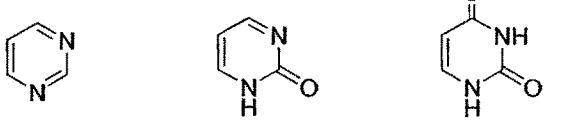


206a

pKa>13
206b

206c

The basic strength of pyrimidinones is greater than pyrimidine because the N atom involved in the cyclic amide formation no longer has the capacity of ring N to attract π-electrons and therefore are less electron withdrawing Thus in uracil, for example, both the N atoms are so involved and protonated that the oxygen atoms are the next available basic centres [486]

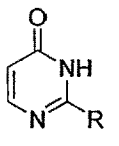


pKa = 1.31
207a

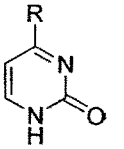
pKa = 9.17
207b

pKa = 9.4
207c

However, there are apparent anomalies in the course of changes in basic strength of aminopyrimidinones/thiones For example, isocytosine (**208a**) is only 0 8 units stronger as a base whereas cytosine (**171c**) is not less than three units stronger than their corresponding pyrimidinones Also, the aminopyrimidines are stronger acids and weaker bases than the corresponding aminopyrimidinones



Isocytosine (**208a**); R = NH_2
Pyrimidinone (**208b**); R = H

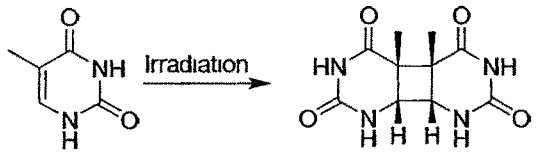


Pyrimidinone (**209**); R = H
Cytosine (**171c**), R = NH_2

3.2.3. Reactivity of pyrimidine

The presence of doubly bound ring N atom reduces the aromaticity of the pyrimidine ring system which results in significant electron depletion at C-2, C-4 and C-6 and relatively minor depletion at C-5. Accordingly the nucleophilic attack will take place at the former positions whereas electrophilic attack will be confined to C-5 or the ring N atoms The insertion of electron withdrawing substituents will increase this effect and electron releasing substituents will decrease it by making all positions more nearly equal.[483] Despite the fact that the C-2, C-4 and C-6 positions are predisposed to direct nucleophilic attack, such example are relatively uncommon [483]

Although the photochemical or free radical reactions in pyrimidine have been studied only to a little extent, the photochemistry of uracil, thymine and related bases has a large and detailed literature because most of the adverse effects produced by UV irradiation of tissues seem to result from dimer (**210**) formation involving adjacent thymine residues in DNA.[487]



Thymine (**171b**) Thymine dimer (**210**)

Various factors like increased reactivity, relative freeness and the steric stress at the attacking site will determine the end products of the electrophilic attack in the pyrimidine ring If sufficient electron donating groups are available, pyrimidines can participate in electrophilic substitution reactions as in the following reactions [483]

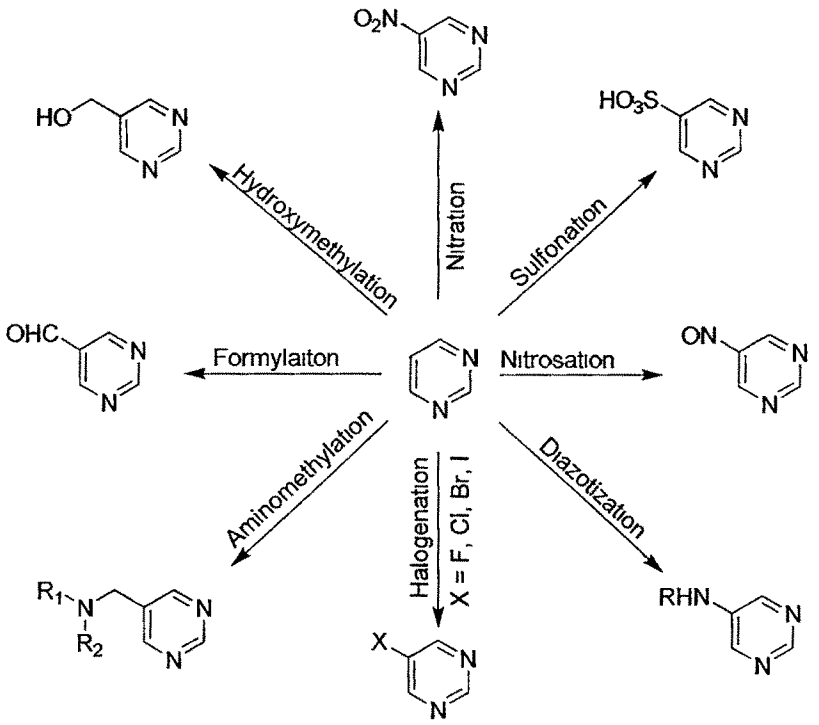


Figure 3.1 Reactions of pyrimidine

3.3. Synthesis of pyrimidine

The synthesis and chemistry of pyrimidines have been discussed by Kenner and Todd[488] in 1957, Ramage and Landquist[489] in 1959 and by Brown[483,484] in 1966 and in 1970. Pyrimidine synthesis by the cyclization of amidines has been reviewed by Miocque et al [490] The subject has been updated, periodically.[491-499] The synthetic methods are classified on the basis of the number of components employed in the pyrimidine cyclization.

3.3.1. Primary synthesis

The first primary synthesis of a pyrimidine from aliphatic fragments was carried out by Frankland and Kolbe in 1848. Since then, a great many quite distinct primary synthetic methods have been devised, although it is true to say that one of these (the 'Principal Synthesis') has provided upward of 80% of all known pyrimidines, either directly or indirectly [483]

3.3.1.1. One component synthesis

This involves the intramolecular cyclization of certain open chain intermediates to yield the pyrimidine nucleus This method can be further classified according to the position of the bond formed during the cyclization [483,484]

Type I	1,2 (2,3) bond formation[500,501]
Type II	3,4 (1,6) bond formation[502]
Type III	4,5 (5,6) bond formation[503]

3.3.1.2. Two component synthesis

This includes distinct synthesis involving condensation of two fragments [483] This category falls naturally into three sub-categories syntheses from [1+5] atom fragments, [2+4] atom fragments and [3+3] atom fragments. Syntheses involving [1+5] atom fragments may be sub-divided into three types in the first, the one-atom fragment supplies C-2 of the final ring, and in the second and third, it supplies N-1 or N-3 respectively. Syntheses involving [2+4] atom fragments may also be subdivided into three types in the first and third, the two-atom fragment supplies C-2 + N-3 or N-1 and C-2 respectively, and in the second, it supplies C-5 + C-6 of the final ring. The last sub-category involves condensation of two fragments with three atoms in each. Different types of this synthesis are depicted as follows

[1+5] atom fragments·

Type IV	C-2	+	N-C-C-C-N[504]
Type V	N-1	+	C-C-C-N-C[484,505-510]
Type VI	N-3	+	C-N-C-C-C[511]

[2+4] atom fragments.

Type VII	C-N	+	C-C-C-N[486,512-520]
Type VIII	C-C	+	C-N-C-N[521-523]
Type IX	N-C	+	C-C-N-C[483,524-527]

[3+3] atom fragments [483,484,514]

Type X	C-C-C	+	N-C-N
Type XI	C-C-N	+	C-N-C

3.3.1.3. Three component synthesis

Very few reports are available for this type of synthesis. Generally, each of the three components, contributes two atoms each comprising [2+2+2] or [3+2+1], for the pyrimidine cyclization.

[2+2+2] atom fragments [483,484,528-532]

Type XII	C-C	+	N-C	+	N-C

[3+2+1] atom fragments [483,533,534]

Type XIII C-C + N-C-N + C

3.3.1.4. Four component synthesis

Synthesis of pyrimidines utilizing this methodology is very uncommon and a few reports are available describing condensation of four fragments to yield a pyrimidine nucleus [483,486,535,536] Examples include synthesis of tetrahydropyrimidines from carbonyl compounds and ammonia or an amine (acetonin synthesis), and a synthesis involving aldehyde, ammonia and a β-dicarbonyl compounds

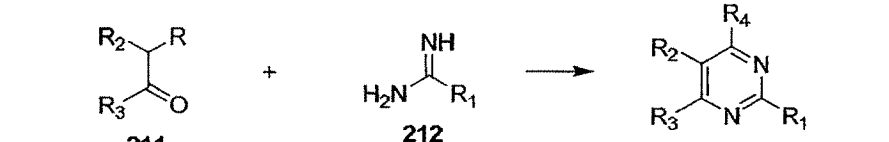
Type XIV C-C-C + N + C + N

3.3.2. Synthesis from heterocycles

A variety of heterocycles have served as starting materials for the synthesis of pyrimidines [483,484,486,514] There have been a few reports on the synthesis of pyrimidines through ring transformations from five membered heterocyclic systems like pyrroles, imidazoles, oxazoles and other six membered heterocyclic systems like pyridines, pyrazines, triazines, oxazines or thiazines Some of the condensed pyrimidine derivatives, such as quinazolines, purines, pteridines and benzofurans have been converted to pyrimidines by oxidative and hydrolytic reactions

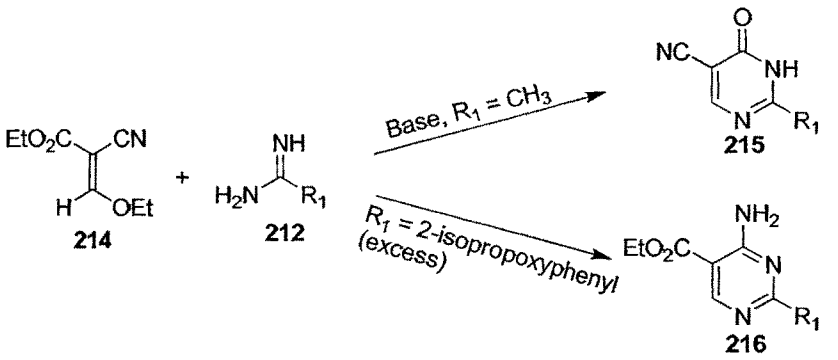
3.3.3. Two component synthesis (*Principal Synthesis*)

This is the most versatile and widely used method of pyrimidine synthesis. It involves the condensation of two reactants One of the components used may contribute three, four or five atoms of the pyrimidine ring system, while the other contributes three, two or one atom, respectively

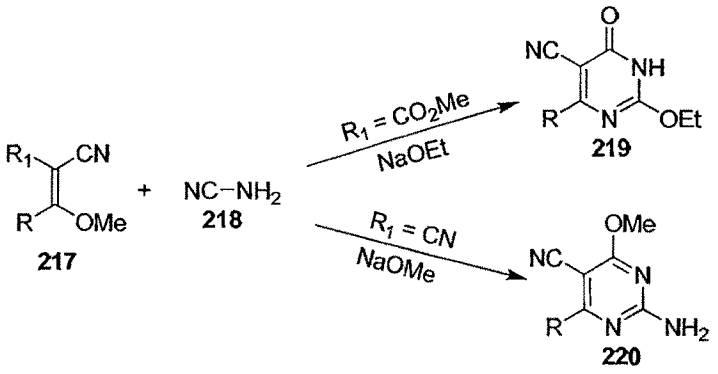


Of the different types of two component synthesis of pyrimidines, the one involving condensation of a three carbon fragment (C-C-C, **211**) with compounds capable of

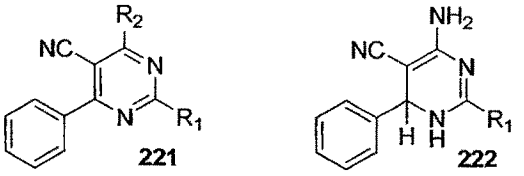
donating an N-C-N fragment (**212**) is the most extensively employed approach towards the pyrimidine ring construction It is appropriately termed as the "Principal Synthesis" of pyrimidines The three carbon fragment, commonly a 1,3-dicarbonyl compound, is condensed with 1,3-binucleophiles (N-C-N fragment). The great versatility of the synthesis lies in the fact that each carbonyl group in the three-carbon fragment can be replaced by an aldehyde, ester, nitrile or imino group (β-dialdehydes, β-aldehydoketones, β-aldehydoesters, β-ketonitriles and β-dinitriles), the 1,3-binucleophiles may be amidine, urea, thiourea, guanidine or any of their O-, S-, or N-alkyl derivatives, and the three-carbon fragment may be substituted at methylene carbon Thus, 2-alkyl or aryl, 2-amino, 2-oxo or 2-mercaptopyrimidines (**213**), have been obtained by employing amidines, guanidines, ureas or thioureas as the corresponding 1,3-binucleophiles, in these condensations [484]



The nature of the product isolated in the reactions of ethyl ethoxymethylenecyanoacetate (**214**) with amidines **212** depends upon the reaction conditions employed [537-539] 5-Cyano-4-oxopyrimidine (**215**) has been obtained by reacting ethyl ethoxymethylenecyanoacetate with acetamidine under alkaline conditions However, 4-amino-5-carbethoxypyrimidine, (**216**, R_1 = isopropyl) has been isolated in the reaction of ethyl ethoxymethylenecyanoacetate with an excess of 2-isopropoxylbenzamidine.[538] Vinylamidine has been isolated as the product of the reaction of ethyl ethoxymethylenecyanoacetate with acetamidine and benzamidines effected at low temperature.[537-539]



Methylisourea reacts with alkoxyalkylidenemalononitrile, to give the expected 4-amino-2-methoxypynmidine.[540] The reaction of alkylidenecyanoacetate (**217**, R_1 = CO_2Me) with cyanamide (**218**) in the presence of sodium ethoxide in ethanol affords the 2-ethoxy-4-oxopyrimidine (**219**) [541] However, similar condensation of alkylidenemalononitrile (**217**, R_1 = CN) with cyanamide (**218**) in the presence of sodium methoxide gave 2-amino-4-methoxypyrimidine (**220**) [540]

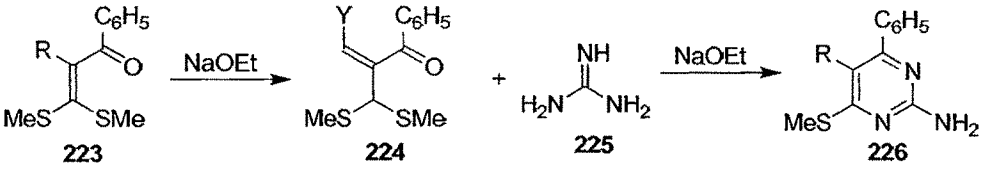


A variety of acrylates and acrylonitrile derivatives with α-bromo-, β-bromo-, β-arylamino- and β-dialkylamino- substituents have been employed as C-C-C fragments in the principal synthesis of pyrimidines [542-546] The use of α,β-unsaturated carbonyl compounds for the condensation with amidines has been reported. The condensation of benzylidene derivatives of cyanoacetic esters and benzoylacetonitrile with amidines in pyridine proceeds with dehydrogenation to afford the corresponding pyrimidine **221**, while the reaction of benzylidenemalononitrile with amidines yields dihydropyrimidine **222** as the only isolable product [547]

The conditions under which the N-C-N and C-C-C fragments can be condensed to form pyrimidines vary with compounds concerned and the variety of conditions has been used Catalyst may be an acid or base, but the choice is depending on the intermediates being used Majority of the condensation reactions seem to proceed best in the presence of bases, which may be either organic or inorganic. However the most common method of carrying out a cyclization to form a pyrimidine ring is to use

sodium ethoxide in refluxing ethanol. Some compounds react together without solvent and without catalyst, for example, guanidine carbonate and acetylacetone give 2-amino-4, 6-dimethylpyrimidine on heating together at 100°C for 30 minutes

The reaction of ketene S,S-acetals derived from various active methylene compounds and 1,3-bisnucleophiles to generate substituted pyrimidines have been excellently reviewed by Dieter[548] and Junjappa [549] The condensation of ketene S,S-acetals derived from cyclic ketones,[550-552] acetophenones,[551-554] malononitrile,[551,555,556] cyanoaceticester,[556,557] aroylacetonitriles,[557] phenylsulfonylacetonitrile,[558,559] methylsulfonylacetonitrile[560] and arylacetonitriles[551,561] with amidines and guanidines has yielded the corresponding 2-(substituted)-6-methylthiopyrimidines Triethylamine, sodium hydroxide, sodium alkoxides or sodium hydride has generally been used as base for the liberation of amidines from their salts in these reactions However, in certain cases, the product formation depends upon the nature and the concentration of the base employed Thus, in the presence of sodium alkoxide, the condensation of ketene S,S-acetals with amidines, guanidines or thioureas leads to formation of 6-alkoxypyrimidines [551,562]

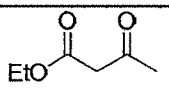
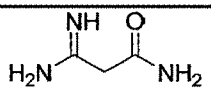
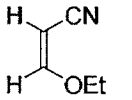
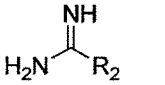
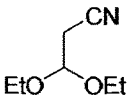
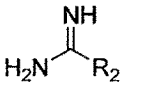
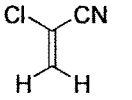
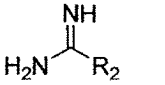
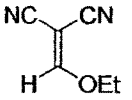
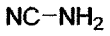
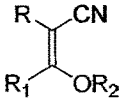
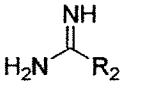
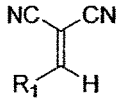
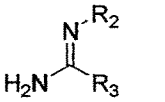
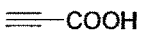
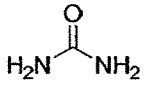
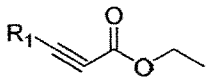
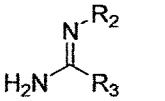
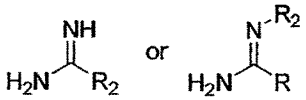
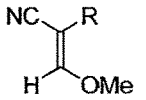
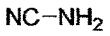
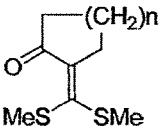
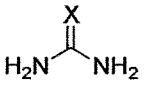
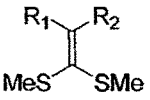
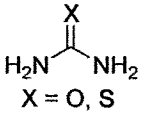


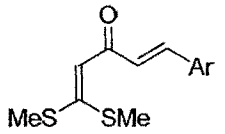
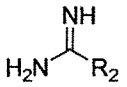
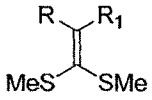
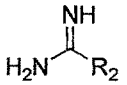
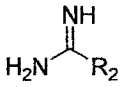
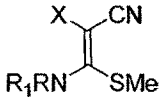
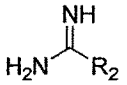
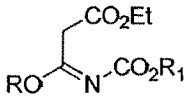
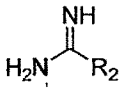
223 224 225 226

The α-ketoketene S,S-acetals (**223**) react with guanidine (**225**) in the presence of sodium alkoxide to yield the 2-aminopyrimidines **226** The formation of pyrimidines in the cyclocondensation has been assumed to involve base induced 1,3-proton migration in the ketene S S-acetals to give intermediate olefin (**224**), followed by its reaction with guanidine [552,563-565]

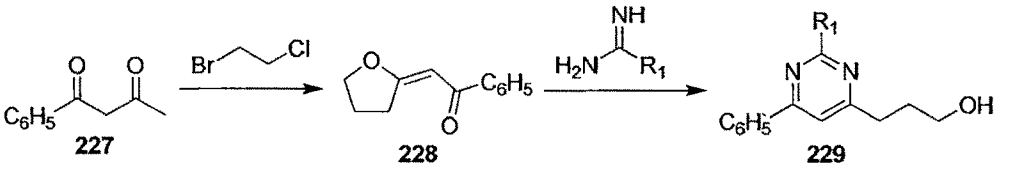
The reaction between the S,N-acetal derived from various active methylene nitriles, such as ethyl cyanoacetate, malononitrile, cyanacetamide and phenylacetonitrile and various amidines have been carried out to synthesize a variety of 4-amino-6-(substituted amino)pyrimidines, under different catalytical conditions. S,N-acetals of ethyl cyanoacetate and cyanacetamide are reported to give 4-oxopyrimidine, with various amidines under basic reaction condition.[551,557-559,563-567] Some examples of the pyrimidine principal synthesis are given in the Table 3 2

Table 3.2 Fragments of Principal Synthesis of pyrimidine

C-C-C fragment	N-C-N fragment	Reference
		568
		569
		569
		569
		570
		571-573
		573
		574
		575, 576
		577, 578
		540, 541
		548-552
		548-552

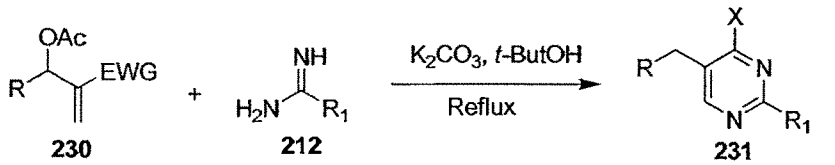
		553, 579
		551, 562-565
		551, 552, 557, 563-567
		551, 552, 557, 562-567
		580

Various modifications based on the conventional method of pyrimidine preparation involving principal synthesis have been reported Different 1,3-dielectrophilic components as C-C-C fragment and amidines as N-C-N fragment have been condensed to yield cyclized pyrimidines [581-585] The reaction of 2-alkylidenetetrahydrofurans (**228**), prepared by cyclization of 1,3-dicarbonyl dianions or 1,3-bissilylenol ethers with various dielectrophiles, provided an efficient access to 4-(3-hydroxyalkyl)pyrimidines (**229**) [581]



227 **228** **229**

Considerable attention has been put into developing solid-phase synthesis of pyrimidines and generation of pyrimidine-containing libraries. In the first approach, this was achieved by condensation of amidines with the support-bound dielectrophiles, such as α,β-unsaturated ketones,[586,587] with the resinbound 2-methylene malonates, followed by oxidation of dihydropyrimidines,[588] with immobilized dialkylaminopropenones,[589,590] cyclic malonate,[591] and γ-ketosulfones.[592] In the last three cases, the products were released from the resin during the condensation. The second approach was to use polymer-bound thiouronium salts or amidines[593,594] which were condensed with acetylenic ketones,[595] activated methylenemalononitriles,[596] β-ketoesters,[597] and ethyl cyanoacetate and aromatic aldehydes [598]

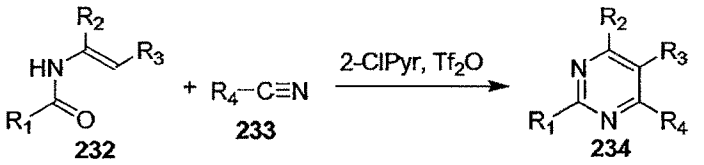


230 **212** **231**

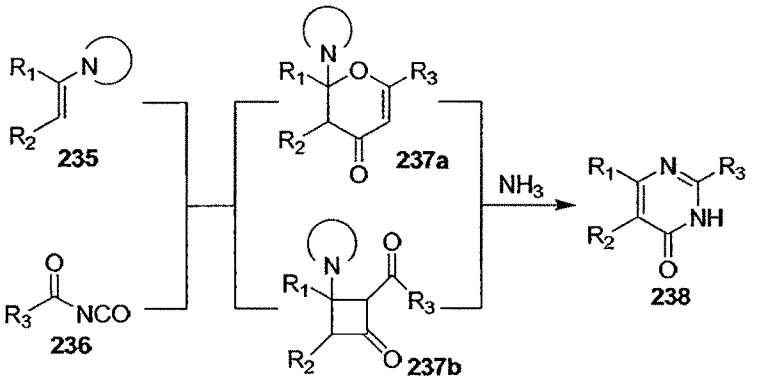
EWG = electron withdrawing groups

X = OH, NH_2, Me

In recent years, some 2,4,5-trisubstituted pyrimidines **231** have been synthesized from the reaction of Baylis-Hillman adducts **230** and amidine derivatives in a one-pot reaction in moderate yields [599-602]

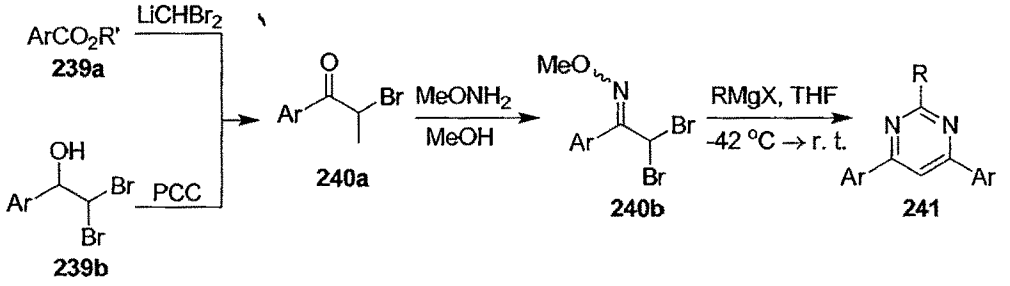


A novel two component single-step and convergent procedure for the synthesis of pyrimidine derivatives has been described by Movassaghi and Hill [603] The unique reactivity associated with electrophilic activation of amides **232** using 2-chloropyridine (2ClPyr) in combination with trifluoromethanesulfonic anhydride (Tf_2O) was efficiently used in this case and subsequent trapping of these highly activated amide derivatives with weakly nucleophilic nitriles **233** directly provided corresponding pyrimidine derivatives **234** The chemistry was applicable to a wide range of secondary amides and nitriles and allowed for unique transformations [603] This methodology not only alleviated the need for isolation of activated amide derivatives but also does not require the additional use of stoichiometric Lewis acids as in other similar cases.[604]

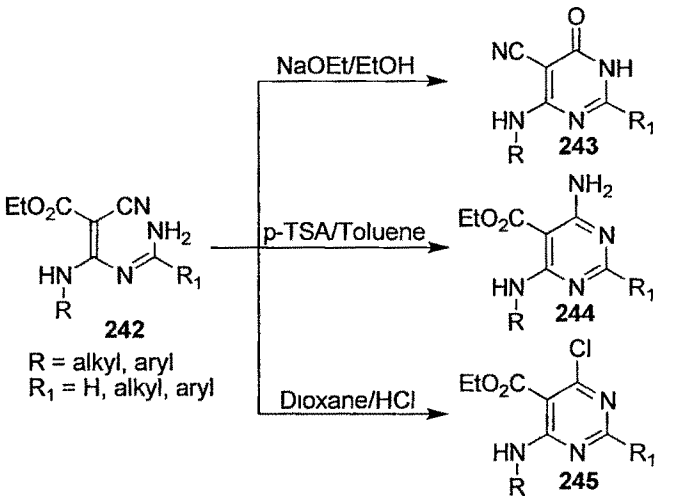


Azetidinones (**237a**) or oxazinones (**237b**), being easily prepared from enamines (**235**) and acyl isocyanates (**236**), were transformed into highly substituted 4(3*H*)-pyrimidinones (**238**) upon treatment with ammonium acetate The entire sequence from enamines to pyrimidinones could be done in one pot without isolation of adducts. This novel ring transformation provides an efficient route to the 4(3*H*)-pyrimidinone ring system [605]

A facile synthesis of pyrimidines from α,α-dibromo oxime ethers with a variety of Grignard reagents has been reported [606] The alkyl or aryl group of a Grignard reagent is efficiently introduced at the 2-position of the pyrimidine core in this reaction.



The mild reaction conditions of the coupling-isomerization sequence of electron-poor (hetero)aryl halides with 1-aryl propargyl alcohols giving rise to chalcones can be extended to a one-pot three component synthesis of 2,4,6-tri(hetero)aryl pyrimidines [607] Similarly, a combinatorial synthesis of a 2,4,5-substituted pyrimidine library using a sequential three component, one-pot reaction has been reported by the use of Suzuki coupling reaction [608]



Synthesis of pyrimidines from the reaction of cyanoketene S,N-acetals and benzamidine is presumed to proceed through difficultly isolable N-cyanovinylamidine Successful isolation of this intermediate under controlled reaction condition has been carried out from our laboratory [502,609-612] N-cyanovinylamidine (**242**) have been converted to various functionalized pyrimidines like 4-oxopyrimidine (**243**), 4-aminopyrimidines (**244**), 4-chloropyrimidine (**245**) by using different catalytical conditions [502,609-612]