CHAPTER 1
PYRIMIDINES: BIOLOGICAL IMPORTANCE AND CHEMISTRY
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1.1 Biological importance of pyrimidines:

Pyrimidines, because of their long history of biological and medicinal significance, occupy unique and important place amongst various heterocycles. Not only they act as building blocks of nucleic acids but they are also used in the therapy against AIDS, cancer and malaria. The synthesis of a variety of pyrimidine derivatives continues to be of interest to the medicinal chemist.

Alloxan, 1, one of the oldest pyrimidine derivative was first obtained by oxidation of uric acid. Alloxan is known for its diabetogenic action in a number of animals. Uracil, 2, thymine, 3 and cytosine, 4, are the three important constituents of the nucleic acids. 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.

Thiamine, 5, a pyrimidine derivative was the first vitamin to be discovered in the Vit.B series.
Notable amongst the drugs having a pyrimidine nucleus are the barbiturates, used in the therapy for a long time for their hypnotic, sedative and anticonvulsant properties. Barbitone (Diethyl barbituric acid, 6) was the first hypnotic to be introduced in medicine in the year 1903.\textsuperscript{7}

In 1948, Hitchings and Elion made an important observation that a large number of 2,4-diaminopyrimidines and some 2-amino-4-hydroxypyrimidines are antagonists of folic acid.\textsuperscript{8} Later it was proved that these pyrimidines are inhibitors of
the enzyme dihydrofolate reductase (DHFR).\textsuperscript{9,10} Notable amongst the 2,4-diamino-pyrimidine drugs are pyrimethamine,\textsuperscript{7} a selective inhibitor of the DHFR of malarial plasmodia. Trimethoprim,\textsuperscript{8} an antibacterial drug which selectively inhibits bacterial DHFR. The very potent, but non selective, DHFR inhibitors, methotrexate,\textsuperscript{9a} and aminopterine,\textsuperscript{9b} are used in cancer therapy.\textsuperscript{11}

\[
\begin{align*}
\text{Sulfadiazine,} & 10, \text{ Sulfamerazine,} 11, \text{ and Sulfadimidine,} 12, \text{ all pyrimidine analogs, are used in acute urinary tract infections, cerebrospinal meningitis and for patients allergic to penicillins with minimum side effects.} 12
\end{align*}
\]

During the last two decades, several pyrimidine derivatives have been developed as chemotherapeutic agents and have found a wide clinical applications. 5-Fluorouracil (5-FU, 13a) and its deoxyriboside (5-FUDR) are potent anticancer agents.\textsuperscript{13,14} 5-Iododeoxyuridine,\textsuperscript{14} is a selective antiviral agent of high selectivity.\textsuperscript{15}
and 5-thiouracil, exhibits some useful antineoplastic activities. 2-Thiourcil, and its alkyl analog, thiobarbital, are effective drugs against hyperthyroidism. Propylthiouracil, is a drug of choice for hyperthyroidism with minimum side effects.

Several condensed pyrimidine derivatives have shown potent antihypertensive activity. Prazocin, a quinazoline derivative, is a selective α₁-adrenoceptor antagonist. Its related analogs, bunazocin, terazocin, and trimazocin are also found to be potent antihypertensive agents. A triaminopyrimidine derivative, minoxidil, a potent antihypertensive is recently introduced in therapy for its side effects in the treatment of alopecia, male baldness.

Recently, some of the 4-arylaminocondensedpyrimidines, have been reported as a potent tyrosin kinase inhibitors.
Besides, there are few examples of pyrimidine antibiotics. The simplest of all is bacimethrin 4-amino-5-hydroxymethyl-2-methoxypyrimidine,19, active against several staphylococcal infections.16 Gourgetin, 20, a cytosine derivative is active against mycobacteria as well as, several Gram positive and Gram negative bacteria.24 Antibiotic tubercidin,21, is reported to exhibit antitumor activity24.

Recently, due to their antiviral effect pyrimidine derivatives have generated widespread interest. Acyclovir,22, at present is the only effective treatment for genital herpes.25
The acquired immuno deficiency syndrome (AIDS) has stimulated a global search for agents active against human immuno deficiency virus (HIV). 3'-Azido-2',3'-dideoxythymidine (AZT, 23) is capable of arresting the retroviruses and at present is the only drug receiving wide clinical usage.26-29 Ara-thymidine (ara-T, 24), is an effective inhibitor of HSV-1, HSV-2, VZV and Epstein-Barr virus.29,30 SAR of pyrimidine nucleosides with antiviral activity has been discussed by Mitsuya et al28,30-34 and Chu et al.36-39
The related orally active fluoroarabino analogue, 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodocytosine, (FIAC) has added advantage over current cytomegalovirus (CMV) therapies. 3'-Fluoro-2',3'-dideoxythymidine, (FddT) has also been reported to have good anti HIV activity with pharmacokinetics similar to AZT in monkey.

Dihydropyrimidines are reported as biologically active molecules. Compound, 27, is reported as a potent Ca-channel blocker with potent and long lasting vasodilative and antihypertensive activity. Recently, angiotensin II antagonistic activity has been reported in pyrimidine 28.

1.2 Chemistry of pyrimidines:

1.2.1 Structure of pyrimidine:

Pyrimidine 29 is the most widely studied diazine containing two nitrogen 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 nitrogen atoms, generally results in a reduced 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.
In addition to this, the electronegative "N" atoms constitute high density centres for the \( \pi \) 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.

1.2.2 The Geometry and Electronic structure of the pyrimidine ring:

The pyrimidine ring is flat. Electron density at the positions ortho and para to the electronegative nitrogen atoms is more in the pyrimidine than the other two diazines, namely 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, the positions C-2, C-4 and C-6 in the pyrimidine ring become strong electropositive centres while the position C-5 retains some electronegativity through only to a lesser extent. At the same time, the localization of \( \pi \) - electrons at the two "N" atoms results in decreased aromaticity of pyrimidine ring. Thus, pyrimidine is not truly aromatic, whatever little semblance of aromaticity is left in the system is at the C-5 position. This decreased stability of pyrimidine which is reflected in the resonance energy of only 26 Kcal/mole in pyrimidine compared to 36 Kcal/mole in benzene. Pyrimidine can be appropriately compared with \( m \)-dinitrobenzene, which too has a lower resonance energy.
The above electron density diagrams in which the distribution of electrical charges i.e. the gain or loss of π-electrons at each atom of the molecule has been calculated for all the three isomeric diazines 30, 31 and 32 by the refined VESCF method (Variable Electronegativity Self Consistent Field Method) further substantiate this point. This localisation of electrons then explains the unique character and basis of pyrimidine chemistry.

1.2.3 pKa of pyrimidine

Pyrimidine is a weaker base (pKa 1.31) than pyridine (pKa 5.2) because the second ring nitrogen shares the available π electrons with the first and the system therefore approximate to 3-nitropyridine (pKa 0.8). Its basicity is intermediate to that of the other two isomeric diazines namely, pyridazine (pKa 2.33) and pyrazine (pKa 0.6) respectively. The insertion of mildly electron releasing methyl group in the ring partly improves this deficiency so that 2-methyl pyrimidine has a pKa of 2.0.

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 a ring
"N" to attract π electrons. Thus in uracil, 2, for example, both the "N" atoms are so involved and protonated that the oxygen atoms are the next available basic centres. On the other hand, the pyrimidinamines are bases of moderate strength because of increase in the resonance of cations 33 and 34 compared to the neutral molecules. Resonance stabilizes the cations thereby increasing the basic strength.

1.3 **Synthesis of pyrimidines**

The synthesis and chemistry of pyrimidines have been discussed by Kenner and Todd in 1957, Ramage and Landquist in 1959 and by Brown in 1966 and in 1970. Pyrimidine synthesis by the cyclisation of amidines has been reviewed by Miocque et al. The subject has been updated, periodically.53-61

Herein, an attempt has been made to cover the recent reports on the synthesis of pyrimidines. The synthetic methods are classified on the basis of the number of components employed in the pyrimidine cyclisations.

1.3.1 **One component synthesis:**

Intramolecular cyclisation of certain open-chain intermediates to obtain pyrimidines are included in this category. The method has been further classified according to the bonds formed in the cyclisation.

- **Type I** 1,2 (2,3) bond formation
- **Type II** 3,4 (1,6) bond formation
- **Type III** 4,5 (5,6) bond formation

1.3.2 **Two component synthesis:**

The pyrimidine synthesis through the condensation of two reactants are discussed in this class. One of the components used in the synthesis may contribute 3,4 or 5 atoms of the pyrimidine ring system while the other component contribute 3,2 or 1 atoms, respectively. Different types of such synthesis are depicted below:
1.3.3 Three component synthesis:

There are only a few reports available on this class of pyrimidine synthesis. All three components contribute two atoms each for the pyrimidine cyclisation as shown below.\(^{65-67}\)

i) Type XII \(\text{C-C} + \text{N-C} + \text{N-C}\)

1.3.4 Synthesis of pyrimidines from other heterocycles:

A variety of heterocycles have served as starting materials for the synthesis of pyrimidines. Some of the condensed pyrimidine derivatives, such as quinazolines, purines and pteridines have been converted to pyrimidines by oxidative and hydrolytic reactions. There have been a few reports on the synthesis of pyrimidines through ring transformations from aziridines, benzofurans, imidazoles, pyrazoles, pyridines, etc.\(^{44,68-71}\)

1.3.5 Two component synthesis:

This is the most versatile and widely used method of pyrimidine synthesis. It involves the condensation of two reactants. One of the component 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 Type IV, involving the condensation of a three carbon fragment with compounds capable of donating a N-C-N fragment and is the most extensively employed approach.
towards the pyrimidine ring construction. It is appropriately termed as the "Principal synthesis" of pyrimidines.65

i) Type IV (C-C-C + N-C-N) : "PRINCIPAL SYNTHESIS"

The condensation of three carbon fragment with N-C-N fragment donor is, generally, referred to as the principal synthesis of pyrimidines. The three carbon fragment used in this synthesis is, commonly, a 1,3-dicarbonyl compound such as β-dialdehydes, β-aldehydoketones, β-aldehydoesters, β-ketonitriles and dinitriles which are condensed with 1,3-binucleophiles. Thus, 2-alkyl or aryl, 2-amino, 2-oxo or 2-mercaptopyrimidines,37, have been obtained by employing amidines, guanidines, ureas or thioureas,36, as the corresponding 1,3-binucleophiles,35, in these condensations.46

The nature of the product in certain condensations of 1,3-dicarbonyl compounds with amidines has been shown to depend upon the reaction conditions employed. Reaction of β-diketone 38 with the diamidine 39 at room temperature
gives the expected pyrimidine 40, while on refluxing in ethanol in presence of base leads the formation of triazolopyrimidine 41.\textsuperscript{42,72-78} 

\[
\text{R}\text{= CO-CH}_2\text{CO- R} \quad \text{H}_2\text{N}\text{= C-NH-NH-C-NH}_2
\]

\[
38 \quad 39
\]

40 41 \( R = \text{CH}_3\text{CH}_2\text{CH}_2^- \)

The reaction of carbamoylacetamidine,\textsuperscript{42} with ethylacetooacetate has been shown to yield the pyridine 44 along with the 2-carbamoylmethylpyrimidine,\textsuperscript{43,79}

\[
\text{H}_2\text{N-C-CH}_2\text{CONH}_2 \quad \text{H}_3\text{C- NCH}_2\text{CONH}_2 \quad \text{H}_2\text{NCO-CH}_3
\]

\[
42 \quad 43 \quad 44
\]

The diaminopyrimidine 48 has been obtained by employing variety of \( \beta \)-aldehyd carbonyl derivatives such as alkoxyacrylonitrile 45, cyanoacetaldehyde diethyl acetal 46 or \( \beta \)-chloroacrylonitrile 47 as 3-carbon fragments.\textsuperscript{80,81}
Ethoxymethylenemalononitrile, when reacted with cyanamide in presence of sodium ethoxide yielded sodium salt of intermediate 50 which on cyclisation in presence of halogen acid gave 4-amino-2-halogeno-5-pyrimidin-carbonitrile. 4-amino-2-halogeno-5-pyrimidin-carbonitrile has been obtained by condensation of substituted alkoxyacrylonitrile with amidines and guanidines. However, the reaction of β-
benzoylalkoxyacrylonitrile, 52 (R=H, R =COC₆H₅) with amidines has been shown to afford 5-cyano-4-phenylpyrimidine,54.98

The nature of the product isolated in the reactions of ethyl ethoxymethylene-cyanoacetate,52, (R = H, R = CO₂C₂H₅, R = C₂H₅) with amidines depends upon the reaction conditions employed.97-99 5-Cyano-4-oxopyrimidine,55, has been obtained by reacting ethyl ethoxymethylene-cyanoacetate with acetamidine under alkaline conditions. However, 4-amino-5-carbethoxypyrimidine,56, (R₂ = isopropyl) has been isolated in the reaction of ethyl ethoxymethylene-cyanoacetate with an excess of 2-isopropoxybenzamidine.98 Vinylamidine 57 has been isolated as the product of the reaction of ethyl ethoxymethylene-cyanoacetate with acetamidine and benzamidines effected at low temperature.97-99

Methylisourea reacts with alkoxyalkyldenemalononitrile,58 (X = CN) to give the expected 4-amino-2-methoxypyrimidine,59.100 The reaction of alkylidene-cyanoacetate,59 (X = CO₂CH₃) with cyanamide in the presence of sodium ethoxide in ethanol affords the 2-ethoxy-4-oxopyrimidine,60.101 However, similar condensation
of alkylidenemalononitrile,58 (X = CN) with cyanamide in the presence of sodium methoxide gave 2-amino-4-methoxypyrimidine,61.100

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.102-112

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 62, while the reaction of benzylidenemalononitrile with amidines yields dihydropyrimidine 63 as the only isolable product.113

Robev114-118 has synthesized a variety of aminopyrimidines through the reaction of N-substituted amidines with aryldienemalononitrile. 3-(Substituted)-4-iminopyrimidines,64, thus obtained, undergo Dimroth rearrangement to afford 4-(substituted amino)pyrimidines,65.
Acetylene carboxylic acids have been employed as three carbon fragments in the principal synthesis of pyrimidines. Thus, uracil, has been obtained in good yields through the condensation of propiolic acid, with urea in benzene in presence of catalytic amount of sulfuric acid.

\[
\text{HC≡C—COOH} + \text{H}_2\text{N—C—NH}_2 \rightarrow \text{2}
\]

Ethyl propiolate, ethyl tetrolate and ethyl phenylpropiolate have been condensed with N-arylacetamidines and were found to yield the 6-unsubstituted, 6-methyl and 6-phenyl-3-aryl-2-methylpyrimidin-4(3H)-ones. The condensation of dimethylacetylenedicarboxylate with acetamidine and trichloroacetamidine under basic conditions gave 6-methoxycarbonylpyrimidine. The reaction proceeds through the isolable vinlamidine intermediate.

\[
\text{NC—CN} + \text{N—R}_3 \rightarrow \text{64}
\]

Dimroth Rearrangement

\[
\text{R}_2\text{H} \rightarrow \text{NH}_2\text{R}_3
\]

\[
\text{NC} \quad \text{N} \quad \text{N—R}_3
\]

\[
\text{R}_2 \quad \text{N} \quad \text{R}_1
\]

\[
\text{65}
\]

Acetylene carboxylic acids have been employed as three carbon fragments in the principal synthesis of pyrimidines. Thus, uracil2, has been obtained in good yields through the condensation of propiolic acid66, with urea in benzene in presence of catalytic amount of sulfuric acid.119

\[
\text{HC≡C—COOH} + \text{H}_2\text{N—C—NH}_2 \rightarrow \text{2}
\]
Dialkyl monothiomalonates have been condensed with amidines. While the reaction of dialkylmalonate, 69, with amidine yields pyrimidin-dione 71, the reaction of monothiomalonate, 70, with amidines affords the 6-alkoxypyrimidine-4-one, 72, as the product. 123

Similarly, enaminothioamide, 73, condenses with amidine salt to form 4-aminopyrimidine, 74. The aminopyrimidine has also been obtained by the reaction of α-oxo-thioamide, 75 with the amidine salt in the presence of a base, such as sodium ethoxide. 124
Acylketene O,O-acetals have been reacted as 3-C donors with amidines to obtain alkoxypyrimidines. Thus, 6-alkoxypyrimidin-4(3H)-one,72, was obtained as the product of the reaction of carbethoxyketene O,O-acetal 76 with amidine.126

\[ \text{H} - \text{CO}_2\text{C}_2\text{H}_5 \]
\[ \text{R}_1\text{O} - \text{OR}_1 \]

76

The condensation of ketene S,S-acetals derived from cyclic ketones,126,127 acetophenones,127 malononitrile,92,93,127-131 cyanoacetic ester,92,130,131 aroylacetonitriles,132 phenylsulfonylacetonitrile,133-135 methylsulfonylacetonitrile136 and aroylacetonitriles127,137 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 77 and 78 with amidines, guanidines or thioureas leads to formation of 6-alkoxypyrimidines,79 and 80, respectively.127,133,138
The 6-alkoxypyrimidine formation in these reactions, presumably, proceeds via the ketene O,S-acetals 81 and 82, formed by the initial reaction of ketene S,S-acetals with alkoxides, followed by their condensation with amidines and guanidines.\(^{127}\)

The \(\alpha\)-ketoketene S,S-acetals 83-85 react with guanidine in the presence of sodium alkoxide to yield the 2-aminopyrimidines 86-90.\(^{139}\)
The formation of the pyrimidines 87-90 has been assumed to involve base induced 1,3-proton migration in the ketoketene S,S-acetals 83-85 to give intermediate olefin of the type 91, followed by its reaction with guanidine.\textsuperscript{139-141}

Junjappa and co-workers\textsuperscript{142} have reported the synthesis of 2,6-diamino-pyrimidines 93 by the condensation of acylketene S,N-acetals 92 with guanidine.
Alternatively, the dianinopyrimidines 93 and 94 have been synthesised from ketene S,N-acetals, 92, derived from acetophenones and ethylcyanoacetate, by sequential reaction with an amine and guanidine.\textsuperscript{142}

Rudoff and Augustin\textsuperscript{132,133} have reported the synthesis of 6-amino- and 2,6-diaminopyrimidines,\textsuperscript{96} through the condensation of α-aryl-α-cyanoketene S,N-acetals 95 with amidines, guanidines and isothioureas.

The reaction between the S,N-acetal 97 derived from various active methylene nitriles, such as ethylcyanoacetate, malononitrile, cyanacetamide and phenylacetonitrile and various amidines have been carried out to synthesise a variety of 4-amino-6-(substituted amino)pyrimidines,\textsuperscript{98} under different catalytical conditions. S,N-acetals of ethylcyanoacetate and cyanacetamide are reported to give 4-oxopyrimidine,\textsuperscript{99} with various amidines under basic reaction condition.\textsuperscript{127,132-138,143-146}
N-alkoxycarbonyliminoether, 100, which can be considered as O,N-acetal in its tautomeric form, has been claimed to yield 6-alkoxycarbonylaminopyrimidine, 101, on condensation with amidine. 147

The use of bistrimethinium salts as C-C-C units in the principal pyrimidine synthesis has been reported. 135 The formation of 4-dialkylaminopyrimidine, 103, from amidine and chlorotrimethinecyanine, 102, represents a variant of classical synthesis. 160
Recently, a new one step method for the synthesis of 2-phenylpyrimidines, 104, was developed by reacting benzotrichloride with various nitriles in the presence of aluminium chloride.181

\[
\begin{align*}
R_2 - H & \xrightarrow{O\!\!=\!\!=N\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\![} \]

Synthesis of pyrimidines from the reaction of cyanoketene S,N-acetals 105 and benzamidine is presumed to proceed through difficultly isolable N-cyanovinylamidine 106. Successful isolation of this intermediate under controlled reaction condition has been carried out from this laboratory.63,182 N-cyanovinylamidine have been converted to various functionalised pyrimidines like 4-oxopyrimidine 107, 4-chloropyrimidine 108, 4-aminopyrimidines 109 by using different catalytical conditions.63,152