CHAPTER 5

NOVEL SYNTHESIS OF 4-BROMOPYRIMIDINES AND CONDENSED 4-BROMO-2-CHLORO/DICHLOROMETHYL-PYRIMIDINES
### NOVEL SYNTHESIS OF 4-BROMOPYRIMIDINES AND CONDENSED 4-BROMO-2-CHLORO/DICHLOROMETHYLPYRIMIDINES

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5.1 Introduction:

5.1.1 Reaction of nitriles under acidic conditions:

Synthesis of a large variety of compounds from nitriles has been carried out under basic conditions. Primarily, these reactions involve nucleophilic attack on the carbon atom of the nitrile group as shown in the scheme I. The reaction has the advantage of generating an imine function which is available for further ring closure.

\[ H^+ B^- + C\equiv N \rightarrow C\equiv NH \]

Scheme I

Direct use of the nucleophilic properties of the nitrile group under acidic conditions in the synthesis of this kind has, however, had its advent only in the early sixties. In this type of reactions the bond formation takes the generalised form as shown in the scheme II.

\[ C\equiv N + A^+ X^- \rightarrow C\equiv N \cdot A \]

Scheme II

The basic difference between the above two types of reactions is that under basic conditions the reaction of the nitrile with a strong nucleophile proceeds via the initial attack on the carbon of the nitrile function (Scheme I). On the other hand, under acidic conditions most of the reactions of nitriles are with electrophilic species, and appear to involve the initial attack on the nitrile nitrogen followed by the combination of the carbon of the nitrile group with the nucleophile available in the medium (Scheme II). The attacking electrophile can be a proton, lewis acid, electrophilic carbon, sulphur or other heteroatoms. These two types of reactions are summarized in the scheme III.
Following are some of the important reactions of nitriles under acidic conditions:

i) With halogen acids nitriles yield imidoyl halide derivatives, \( 211 \):

\[
R-CN + H^+ \rightarrow R-C=NH^+ \rightarrow R-C=NH \quad \text{(Acidic Medium)}
\]

\[
R-CN + H^+ \rightarrow R-C=N^+ \rightarrow R-C=N^+ \rightarrow R-C=NH \quad \text{(basic Medium)}
\]

\[
R-CN + H^+ \rightarrow R-C=N^+ \rightarrow R-C=NH \quad \text{(basic Medium)}
\]

ii) In the Ritter reaction, \( 303 \) nitriles are reacted with alcohols to obtain amides, \( 212 \):

\[
R_3COH \rightarrow R_3CO^+ \quad \text{(Acidic Medium)}
\]

\[
R-CN + CR_3 \rightarrow R-CNCR_3 \quad \text{(basic Medium)}
\]

\[
R-CN + CR_3 \rightarrow R-CNCR_3 \quad \text{(basic Medium)}
\]

iii) With acid halides nitriles yield N-acylimidoylhalides, \( 304,305 \) and

\[
R-CN + R-C=O^+ \rightarrow R-CNCR_3 \quad \text{(basic Medium)}
\]

\[
R-CN + R-C=O^+ \rightarrow R-CNCR_3 \quad \text{(basic Medium)}
\]
iv) With sulfonyl chlorides nitriles yield chlorosulfinimines.\textsuperscript{214,306}

\[
\begin{align*}
R\cdots C=\text{N} & \xrightleftharpoons{\text{S}^+} R\cdots C=\text{N}^+ \text{ SR'} \xrightleftharpoons{\text{Cl}^-} R\cdots C=\text{N}-\text{SR'} \\
\text{Cl} &
\end{align*}
\]

5.1.2 The imidoyl halides:

The polar $C=\text{N}$ group of the nitriles is prone to electrophilic attack at the nitrogen and nucleophilic attack at the carbon. The interaction of a nitrile\textsuperscript{215} with an acid or its complexation with a Lewis acid leads to the formation of a species\textsuperscript{216} possessing greater electrophilicity. Therefore, many of the reactions of nitriles with nucleophilic reagents are acid catalysed. Halogen acids are particularly effective in promoting the reactions of nitriles with a variety of nucleophiles.

\[
\begin{align*}
R\cdots C=\text{N} + \text{A}^+ & \rightarrow R\cdots C=\text{N}^- \text{A}^- \\
\text{215} & \quad \text{216}
\end{align*}
\]

In the absence of other nucleophilic species, nitriles react with halogen acids to yield unstable adducts of different compositions. The nature of these adducts, as well as the possible involvement of such nitrile-halogen acid adducts in the hydrogen halide catalysed reactions of nitriles with nucleophiles, has been the subject of considerable discussion.\textsuperscript{302-311}

The reactions of halogen acids with nitriles yield products of varying compositions, such as $\text{RCN.HX}$, $2\text{RCN.HX}$, $2\text{RCN.nHX}$, etc. A variety of aliphatic and aromatic nitriles with halogen acids, at low temperatures, have been found to yield adducts of the general composition $\text{RCN.2HX}$, which are assigned the imidoyl halide hydrohalide structure\textsuperscript{217}, based on their physical and spectroscopic properties.\textsuperscript{304,308,312-316}

\[
\begin{align*}
R\cdots C=\text{N.HX} & \\
\text{X} & \\
\text{217}
\end{align*}
\]

The formation of an imidoyl halide hydrochloride from a nitrile can be...
depicted as shown in scheme IV. The protonation of the nitrile yields the nitrilium ion 218 which combines with a halide ion to form an imidoyl halide 219. Being sufficiently basic the imidoyl halide 219 reacts with another molecule of the halogen acid to yield the imidoyl halide hydrohalide salt 220.

\[
\begin{align*}
\text{R—C=NH}^+ & \quad \text{X}^- \\
\text{R—C=NH} & \quad \text{X} \\
\text{R—C=NH}^+ & \quad \text{HX} \\
\end{align*}
\]

Scheme IV

In general, the imidoyl halide 219 of the composition RCN.HX are not isolable from the reaction of nitriles with hydrogen halide due to their unstable nature, though a few claims are made on their isolation. In most of the cases, they are isolated as salts. Certain aromatic nitrile-tetrachloride adducts on reaction with hydrogen chloride under appropriate conditions yield isolable nitrilium salts 221.

\[
\begin{align*}
\text{R—C=NH}^+ & \quad \text{SnCl}_6^{2-} \\
\end{align*}
\]

A few reports on the isolation of dimeric salts of the composition 2RCN.HCl are also available. Thus, \(\alpha\)-chloroacetonitriles with hydrogen chloride in solvent ether yield salts of the compositions 222 & 223. This unstable acetimidoyl...
chloride has been found to undergo slow transformation to a dimeric salt of the composition $2\text{CH}_3\text{CN}:2\text{HCl}$. \(^{312}\)

\[
\begin{align*}
\text{NH} & \quad \text{Cl} \\
\text{R} & \quad \text{C} \quad \equiv \quad \text{N} \quad \equiv \quad \text{C} \quad \text{R}
\end{align*}
\]

\[
\text{222}
\]

Such 2:2 adduct formation has also been observed in the reaction of chloroacetonitrile with hydrogen chloride. These 2:2 adducts have been assigned the structure, $^{224,319}$

\[
\begin{align*}
\text{NH} & \quad \text{Cl} \\
\text{R} & \quad \text{C} \quad \equiv \quad \text{N} \quad \equiv \quad \text{C} \quad \text{R}
\end{align*}
\]

\[
\text{223}
\]

Only a few reactions of the isolated nitrile-halogen acid adducts have been investigated. Their reaction with alcohols, amines, and water leads to the formation of the corresponding imidates, amidines and amide derivatives. \(^{302}\) The dimeric imidoyl halides react with phosgene to yield dichloropyrimidines. \(^{307}\)

Though only a few reactions of the isolated nitrile halogen acid adducts have been studied, nitrilium salt 218, imidoyl halide 219, imidoyl halide hydrochloride 220 and the dimeric salt 222 have been proposed as the transient intermediates in a variety of reactions of nitriles with nucleophiles, in the presence of halogen acids. \(^{302,307,310,316,320}\) The role of protonated nitriles or imidoyl halide derivatives is established in a variety of important synthesis.

Nitriles react with alcohols in the presence of hydrogen chloride to give imidate hydrochloride 225 through the transient intermediate, imidoyl halide.
Imidoyl chloride derivatives, in equilibrium with nitrilium chloride salts, are presumably the active intermediates involved in Gattermann and Houben-Hoesch synthesis of aldehydes and ketones. This synthesis involves the reactions of HCN or other nitriles with an arene or a phenol and are conducted in the presence of dry HCl gas and an electrophilic metal halide. Improved yields of ketenimine derivatives have been obtained in the Hoesch reaction by the prior preparation of imidoyl chloride salts, followed by their reaction with phenols.

5.1.3 Intramolecular cyclizations of functionalised nitriles to azaheterocycles:

A variety of heterocycles are synthesised by the intramolecular cyclizations of appropriately functionalised nitriles. Johnson and Madronero have reviewed the synthesis of azaheterocycles by the intramolecular cyclization of functionalised nitriles under acidic conditions. Halogen acids have been found particularly effective cyclizing agents in such acid catalysed heterocyclization reactions. A few examples of such cyclisation are listed below.
Reaction of hydrogen bromide with succinonitrile \(228\) leads to the formation of the 2-bromopyrrole hydrobromide \(229\), which hydrolyses to pyrrolidinone \(230\).

\[
\text{NC-CH}_2-\text{CH}_2-\text{CN} \xrightarrow{\text{HBr}} \text{Br} \quad \text{H}_2\text{O} \quad \text{NC-CH}_2-\text{CH}_2-\text{CN}.
\]

The reaction of cyanogen with an aldehyde in the presence of hydrogen chloride has been found to yield 4,5-dichloroimidazole. The reaction, presumably, proceeds via the cyclisation of the imidoyl halide \(231\) with the aldehyde to give \(232\), which tautomerizes to dichloroimidazole \(233\).

\[
\text{NC-CN} \xrightarrow{\text{HCl}} \text{Cl} \quad \text{RCHO} \quad \text{Cl} \quad \text{Cl} \quad \text{R}
\]

The reaction of \(\alpha\)-mercaptoacrylonitriles and their analogues with halogens has provided a facile method for the preparation of 3-haloisothiazoles. Reacting mercaptopropionitrile \(234\) with chlorine, 3-chloroisothiazole \(235\), has been obtained in 66% yield as the reaction product.
Dinitrile cyclisation with hydrogen bromide has been applied to the cyclisation of 2-cyanoalkylthiocyanates 236 to obtain the salts of 2-bromo-4-aminothiazoles 237 in excellent yields. In certain cases, some of the aminothiazoles have been isolated as acetyl derivatives.301

\[
\begin{align*}
\text{CN} & \quad \text{N} \\
\text{S} & \quad \text{Br}
\end{align*}
\]

On treatment with halogen acids, β-ketonitriles or their analogues, generally lead to the formation of 2-halopyrimidines.301,317-328,330 Thus, methyl methoxyvinylmethyleneacetoacetate,238, on treatment with hydrogen chloride, at room temperature has yielded methyl 2-chloronicotinate,239.331

\[
\begin{align*}
\text{CH}_3 \text{O} & \quad \text{CN} \\
\text{CO}_2\text{CH}_3 & \quad \text{Cl}
\end{align*}
\]

Various substituted aminobutyronitrile 240 with hydrogen chloride afforded 2-iminopyrrolidine hydrochloride (241, n=1) by the intramolecular cyclization with the concomitant loss of alkyl group as alkyl chloride.332,333
Recently, the isolation of 3-(aminoalkylidene amino)-3-aryl-2-propenenitriles, 242, and their transformation to 2-(o-aminoalkyl)-6-aryl-4-halo-5-pyrimidine-carbonitriles, 243, in presence of various haloacids in acetic anhydride has been reported. 244

\[
\begin{align*}
R_1 &= \text{Substituted aryl} \; ; \\
R_2 &= \text{CN} \\
X &= \text{Cl, Br, I}
\end{align*}
\]

A variety of o-aminonitriles 244 has been cyclised to give condensed 4-oxopyrimidines 246 by employing hydrogen chloride in different solvents. 245 This reaction presumably proceeds via the initial protonation of the nitrile function, followed by the cyclization of the protonated species to an oxazine 245 which undergoes a Dimroth rearrangement during the workup of the reaction mixture, to yield the condensed 4-oxopyrimidine 246 as the final product.

\[
\begin{align*}
\text{C\equiv N} & \xrightarrow{\text{HCl}} \text{NH} & \text{O} & \xrightarrow{\text{R}} \\
244 & & 245 & & 246
\end{align*}
\]

Oxazine (248, X=O) and thiazine (248, X=S) are the presumed intermediates in the hydrogen chloride or hydrogen bromide catalysed condensation of o-aminonitriles 247 with dimethyl formamide, dimethyl acetamide and thioamides to
yield the condensed pyrimidines 249. Thus, functionalised nitrile derivative possessing an appropriately placed electrophilic carbon or a hetero atom can undergo analogous reactions intramolecularly to yield a cyclic imidoyl derivative. Indeed, a variety of such functionalised nitriles have been cyclised to form nitrogen heterocycles. When affected under the influence of halogen acids, halogens and other halide donors, cyclisations have yielded, the cyclic imidoyl halide as the product of the reaction. A variety of halogenopyrroles, imidazoles, isothiazoles, thiazoles, triazoles, pyridines, pyrazines, triazines and their condensed analogs, which can be considered as cyclic imidoyl halides, have been prepared, essentially by this approach.

5.1.4 Synthesis of condensed pyrimidines through the reaction of nitriles with α-amino carboxyl compounds:

The intramolecular condensation of a nitrile with a substrate possessing electrophilic and nucleophilic centers often leads to the direct formation of an aza-heterocycle by the incorporation of the C≡N moiety of the nitrile in the ring. Such a condensation could, conceivably, proceed by a concerted cycloaddition process (type A) or by discreet steps, involving either the initial electrophilic attack on the nitrile nitrogen (type B) or by the initial nucleophilic attack at the nitrile carbon (type C), followed by the ring closure (Scheme V). Such a heterocyclic synthesis from nitriles has been briefly reviewed by Meyers and Sircar.
Many of the reactions of nitriles with substrates containing an oxygen, sulphur, nitrogen or carbon nucleophilic center and an appropriately placed electrophilic group capable of undergoing cyclization, lead to heterocycle formation of type 'c' pathway. Thus, the reaction of o-aminocarbonyl compounds 250, (such as o-aminoketones, o-aminoesters, o-aminoamides and o-aminonitriles) with a nitrile should, in principle, lead to the formation of condensed pyrimidines 251.

Cyclisation of appropriate o-aminocarbonyl compounds with the nitrile derived reagents like amides, thioamides, imidates and amidines to a variety of quinazolines and condensed pyrimidines have been reported.338,342-344

Earlier, condensed pyrimidines have been obtained by the condensation under basic conditions at elevated temperatures.345 A few quinazolin-4-one derivatives have been obtained by the reaction of nitriles with anthranilic acids or
esters in the presence of bases. 2-Methylquinazolin-4-one 253 has been obtained in low yield by heating a mixture of anthranilic acid 252 and acetonitrile in a sealed tube.

Similarly, the reaction of anthranilic acid 252 with a wide variety of nitriles at higher temperature was found to yield 4-oxoquinazolines in poor yields. Catalytic effect of an acid in such condensations was observed to enhance the yield. Thus, o-aminobenzamide hydrochloride,254, on reaction with acetonitrile, propionitrile and benzonitrile in a sealed tube at 200°C yielded the corresponding quinazolines (255, R=CH₃, C₂H₅, C₆H₅) in about 20% yields, while o-aminobenzamide base itself yielded only less than 6% of the desired quinazolines.

5.1.5 One-pot synthesis of condensed pyrimidines:

Methyl-5-chloroanthranilate on refluxing with excess of acetonitrile or benzonitrile in the presence of dry HCl gas yielded 2-methyl and 2-phenyl-6-chloro-1,4-dihydroquinazolin-4-one 256.
Catalytical excess of dry HCl gas in acetic acid has been used for the condensation of methyl anthranilate\textsuperscript{257}, with ethylcyanoformate to obtain 2-carbethoxyquinazolin-4-one\textsuperscript{258}.\textsuperscript{354}

The increased reactivity of nitriles in the presence of acids has been exploited in this laboratory for the synthesis of condensed pyrimidines. Nitriles have been reacted with a variety of o-aminocarbonyl compounds. This novel approach has led to the development of a facile, one-pot synthesis of condensed pyrimidines of general applicability.\textsuperscript{152,355,356} Thus, a variety of o-aminocarbonyl compounds such as o-aminoketones \textsuperscript{259a}), o-aminonitriles \textsuperscript{259b}, o-aminoesters \textsuperscript{259c}, and o-aminoamides \textsuperscript{259d} have been reacted with nitriles to obtain the 4-substituted condensed pyrimidines \textsuperscript{260a-d}, respectively (Scheme VI)
Anthranilic acid ester 261 and ω-aminoesters of thiophene 262 and 263 benzothiophene 264, pyrido thiophene 265 and isothiazole 266 have been found to react with a variety of aliphatic, aromatic and heterocyclic nitriles in the presence of dry hydrogen chloride gas to yield the corresponding condensed 4-oxopyrimicines 255, 267-271 (Scheme VII). 

Scheme VI
Scheme VII
The reaction consists essentially of bubbling the dry hydrogen chloride gas into the mixture of a nitrile and o-aminoesters in dioxane at ambient temperature for 4-8 hrs., followed by the usual work-up to isolate the condensed pyrimidin-4-one. The same reaction has been simplified by stirring the mixture of a nitrile and o-aminoesters in dioxane saturated with dry HCl gas at ambient temperature for 4 hrs., followed by the usual work-up to isolate the condensed pyrimidin-4-one. Dioxane and acetic acid appear to be convenient solvents in this reaction as they have capacity to absorb large quantity of hydrogen chloride gas. The yields of the pyrimidines obtained have been found to be unmatched by any of the reported methods to obtain such condensed pyrimidines from o-aminoesters.

It appears likely that the initial reaction is between the nitrile or the imidoyl halide derivative derived from the nitrile and hydrogen chloride, and the amino function of 259c, to yield the amidine intermediate 272 which cyclizes intramolecularly to yield the pyrimidine 260c as the product of the reaction (Scheme VIII). In fact, isolation of these amidine intermediates under controlled reaction conditions have been reported from our laboratory.

Recently, anthranilonitrile 273 has been reacted with formic acid in the presence of sulfuric acid or methylsulfonic acid to obtain quinazolin-4(H)-one 274, instead of 4-aminoquinazoline. The reaction proceed through rapid hydrolysis and N-formylation with formic acid followed by cyclisation or dehydration.
The condensation of anthranilic acid \(\text{275}\), with acetonitrile and phenylacetonitrile has yielded the 4-aminoquinazolines \(\text{276}\). Similar reactions of thiophene \(\text{o-aminonitrile,277}\), with acetonitrile, phenylacetonitrile, benzonitrile and ethyl cyanoacetate yield the corresponding 4-aminothieno(2,3-d)pyrimidines,\(\text{278}.^ {255,257,267}\)

Furan \(\text{o-aminonitrile,279}\), pyrrole \(\text{o-aminonitrile,280}\), 3-amino-4-cyanothiophene,\(\text{281}\), 3-amino-4-cyanoisothiazole,\(\text{282}\), react with acetonitrile to yield the corresponding condensed pyrimidine \(\text{283-286}.^ {255,257,267}\) (Scheme IX)
Molina et al have reacted pyrido[1',2':1,5]pyrazolo-9-aminonitrile, 287, with simple nitriles in presence of dry hydrogen chloride to obtain 1-amino-7,9-diphenylpyrido[1',2':1,5]pyrazolo(2,3-d) pyrimidines 288. 346
Amidine intermediates 290 have been isolated by Eger et al, in the reaction of pyrrole α-aminonitrile, 289, with acetonitrile as well as cyanamide under influence of dry HCl gas. These amidines have been thermally cyclized to the condensed pyrimidines 291.

Interestingly, when haloacetonitriles and the related nitriles possessing electron withdrawing groups, are reacted with α-aminonitriles 292, the reaction proceeds in an unexpected manner to yield the condensed 4-chloropyrimidine. Thus, chloroacetonitrile and dichloroacetonitrile were found to react with anthranilonitrile, thiophene α-aminonitriles and furan α-aminonitrile to give corresponding 2-substituted-4-chloropyrimidines 293 as the only isolable product in excellent yields.
On the other hand, ethylcyanoformate, when condensed with thiophene α-aminonitrile, has yielded a mixture of 4-amino and 4-chloro-2-carbethoxythienopyrimidines 294 and 295, respectively. Similar mixtures of the corresponding condensed 4-amino and 4-chloropyrimidines 296 and 297 have been obtained in the condensation of thiophene α-aminonitrile 277 with phenylthio- and phenoxyacetonitrile; and furan α-aminonitrile 279 with phenylsulfonylacetonitrile.
This one-pot formation of 4-chloropyrimidines is indeed novel, especially, in view of the fact that 4-chloropyrimidines are normally prepared through multistep synthesis, involving the preparation of the corresponding 4-oxopyrimidine, followed by the chlorination with POCI₃.

5.2 Aim of the present work:

4-(Substituted amino)pyrimidines and condensed 4-(substituted amino)pyrimidines are known to exhibit a variety of biological activities. 4-Halo substituents in pyrimidines are prone to substitution by amines. In general, the ease of various halides to undergo nucleophilic substitution by various amines follows the order I>Br>Cl>F.

A few reports are available on the synthesis of 4-bromopyrimidine and condensed 4-bromopyrimidines. Available methods involve bromination of the corresponding hydroxypyrimidine using reagents like phosphoruspentabromide, phosphoroustri bromide, phosphorusoxybromide or combination of these reagents. Application of these reagents however, involves multistep reactions.
In the present study, we report a novel, environment friendly one pot reaction for the synthesis of 4-bromopyrimidines and condensed 4-bromopyrimidines.

5.3 Results and Discussion:

5.3.1 Synthesis of 4-bromopyrimidines by intramolecular cyclisation of N-cyanovinylamidine:

A one pot method has been developed to synthesise 4-bromopyrimidines. 4-Bromopyrimidines have been synthesised through novel approach which involves intramolecular cyclisation of an intermediate N-cyanovinylamidines in the presence of dry hydrogen bromide gas. Isolation of N-cyanovinylamidines, otherwise difficultly isolable intermediates in the synthesis of pyrimidines, were obtained by the reaction of α-cyanoketene S,N-acetals with different amidines namely formamidine (chapter II), acetamide and benzamide under controlled reaction conditions.

The title compounds were obtained by stirring 0.01 mol of N-cyanovinylamidine in 30ml of 1,4-dioxan previously saturated with dry hydrogen bromide gas (6M) for 2hrs and allowing the reaction mixture to stand at room temperature for 2 h. Workup of the reaction mixture after pouring it into ice gave a light yellow coloured compound in good yield, as the only product. The I.R. spectrum of the product was devoid of nitrile stretching absorption around 2200 cm\(^{-1}\), indicating the participation of the nitrile function in the cyclisation. However, the I.R. and \(^1\)H NMR spectra of the product indicated the absence of a primary amino group. The mass spectrum of the product exhibited a prominent molecular ion peak and an intense M+2 peak confirming the presence of bromine in the molecule. Based on microanalysis and spectral data the product was assigned the structure as 4-bromo-5-carbethoxy-6-(substituted amino)-2-(substituted)pyrimidine. All N-cyanovinylamidines were found to cyclize to the corresponding 4-bromopyrimidines in the similar manner. (Scheme X; Table 5.1)
The cyclisation of cyanovinylimidoyl derivatives with hydrogen bromide appears to be a facile route to the synthesis of 4-bromopyrimidines. The method offers an attractive alternative for the preparation of 4-bromo-6-(substituted amino)pyrimidines which are otherwise accessible only through multi step synthesis. A plausible mechanism for this novel interesting transformation is presented in the scheme X.

Scheme X

\[ \begin{align*}
\text{HN} & \quad \text{R}_1 \quad \text{298} \\
\text{HN} & \quad \text{N} = \text{C} = \text{N} \quad \text{R}_2 \\
\text{H}_5\text{C}_2\text{O}_2\text{C} & \quad \text{C} = \text{O} \quad \text{N} \\
\text{HBr} & \quad \text{Dioxan} \\
\text{HN} & \quad \text{R}_1 \\
\text{NH}_2 & \quad \text{R}_2 \\
\text{H}_5\text{C}_2\text{O}_2\text{C} & \quad \text{C} = \text{N} \quad \text{NH}_3 \\
\text{Br} & \quad \text{Br} \\
\text{R}_1 & \quad \text{Phenyl or Substituted Phenyl} \\
\text{R}_2 & \quad \text{C}_6\text{H}_5, \text{CH}_3, \text{H} \\
\end{align*} \]
5.3.2 Physical and spectral characteristics of 4-bromopyrimidines:

The 4-bromo-6-(substituted amino)-2-(substituted)-5-carbethoxypyrimidines are pale yellow coloured crystalline solids having low melting point compare to 4-chloro-pyrimidines. They are freely soluble in most of the organic solvents except n-hexane from which all the compounds were recrystallised.

U V Spectra :

In the U V spectrum of the 4-bromo-2-unsubstituted and 4-bromo-2-methylpyrimidines absorb between 208 nm-217 nm (log ε 4.6) and 278 nm-285 nm (log ε 4.2) respectively, while 4-bromo-2-phenylpyrimidines exhibits longer wavelength absorption between 212 nm-216 nm (log ε 4.5), and 285 nm (log ε 4.2).

I R Spectra :

The hydrobromic acid catalysed reaction of N-cyanovinyformamide shows absence of C≡N peak at 2200 cm⁻¹ thereby indicating the intramolecular cyclisation of this intermediate. The 4-bromo-5-carbethoxypyrimidines exhibit a weak N-H band at around 3270 cm⁻¹ of aromatic amino group at 6th position. The C=O stretching absorptions in these pyrimidine derivatives are observed at around 1680-1670 cm⁻¹. This downward shift of carbonyl peak is due to the intramolecular hydrogen bonding with secondary amino group.

¹H NMR Spectra :

The ¹H NMR spectra of 4-bromopyrimidines exhibited a sharp singlet in the region of δ 9.7 - 10.0 of aryl substituted amino proton. A triplet at δ 1.3 and quartet at δ 4.3 confirms the presence of ethyl moiety of carbethoxy group. 4-Bromo-2-(unsubstituted)pyrimidines 299a-e show a sharp singlet at δ 8.4 corresponding to one proton at C-2, while in case of 4-bromo-2-methylpyrimidine 299f-h shows sharp singlet at δ 2.6 corresponding to three protons of methyl group at 2nd position. 2-Phenylpyrimidines 299i-h have shown multiplets in the region of δ 7.5-8.5 corresponding to ten protons due to the phenyl rings of C-2 and C-6. Other 4-
bromopyrimidines have shown multiplets in the region of δ 7.1 - 7.6 due to the phenyl ring at C-6.

**MASS Spectra:**

Intense molecular ion and prominent M+2 peaks characterise the mass spectra of various 4-bromopyrimidines 299a-e (R=H), 299f-h (R=CH₃), 299i-(R=C₆H₅). 6-Anilino-4-bromo-5-carbethoxy-2-phenylpyrimidine, 299i shows intense ion peak at m/e 352 which is due to McLafferty rearrangement and the loss of C₂H₅OH from molecular ion. The loss of Br⁻ from the radical cation (m/e 352) leads to the cation m/e 272 as moderately intense peak. Major decomposition pathway of the ions m/e 352, 324, 272, and 244 appears to be the loss of neutral molecule C₆H₅CN to yield the ions m/e 249, 221, 169, 141 respectively (Scheme XI). Similar fragmentation pattern was observed in the spectra of 4-bromopyrimidine 299a and 299f.
Scheme XI
5.3.3 Synthesis of condensed 4-bromo-2-chloro/dichloromethylpyrimidines through the reaction of nitriles with various o-aminonitriles:

The enhanced reactivity of nitriles towards nucleophiles in the presence of acids, particularly halogen acids, is known. However, utilisation of the enhanced reactivity of nitriles in the presence of acid for the synthesis of condensed pyrimidines through the reaction with o-aminocarbonyl compounds, has, hitherto, remained unexplored.

Synthesis of various condensed pyrimidines from o-aminocarbonyl compounds with various nitriles in presence of dry hydrogen chloride gas by novel one pot reaction has been reported from this laboratory. Formation of 4-chloropyrimidine in the reaction of various o-aminonitriles with halogenoacetonitriles in presence of dry hydrogen chloride gas has been first reported from this laboratory.

It was, therefore, thought of interest to study the effect of hydrogen bromide in the formation of condensed pyrimidines. Here we hypothesised that o-aminonitrile with halogenoacetonitrile in presence of hydrogen bromide should give condensed 4-bromo-2-halogenomethylpyrimidine. Formation of 4-bromopyrimidine will provide additional proof to the earlier proposed mechanism of the formation of the 4-chloropyrimidines. As bromide ion is better leaving group than chloride, it is easy to displace 4-bromo with amines to get 4-substituted aminopyrimidines, which are biologically important pharmacophore.

The reaction of o-aminonitriles with nitriles like acetonitrile, benzonitrile, phenylacetonitrile in the presence of halogen acid are reported to give exclusively 4-aminopyrimidines while the reaction of o-aminonitriles with halogenoacetonitrile in presence of halogen acid yielded exclusively 4-halopyrimidine. In present study we have used dry HBr gas as halogen acid. The exclusive formation of 4-bromopyrimidines over that of 4-aminopyrimidines can be rationalised as occurring through the preferential cyclisation of the initially formed amidine intermediate, by the pathway which may be attributed to the increased electrophilicity of the amidine carbon and the decreased nucleophilicity of the amidine nitrogen in the intermediate, as a consequence of the electron withdrawing effect of bromine atom. (Scheme XII).
Condensed 4-bromopyrimidines 304 were synthesised by novel one pot reaction. The reaction was carried out by stirring various o-aminonitriles 302 with halogenoacetonitriles 303 in presence of dry hydrogen bromide gas in dioxan for 2 hrs and allowing reaction mixture to stand at room temperature for 2hrs. (Scheme XIII) Workup of the reaction mixture after pouring it into ice-water mixture gave light yellow coloured compound as the only product in good yield. This one-pot reaction is a facile method for the synthesis of 4-bromocondensed pyrimidine.
The I.R. spectrum of the product was devoid of C≡N stretching absorption around 2200 cm⁻¹, indicating the participation of the nitrile function in the cyclization. However, the I.R. and ¹H NMR spectra of the product indicated the absence of a primary amino group confirms exclusive formation of 4-bromopyrimidines. The mass spectrum of the product exhibited a prominent molecular ion peak and an intense M+2 peak suggesting the presence of bromine in the molecule. Moreover, the compounds analysed for its elemental analysis. Based on these observations the product was assigned the structure as 4-bromo-2-chloro/dichloromethyl-condensedpyrimidine. All o-aminonitriles were found to react with various halogenoacetonitriles to the corresponding condensed 4-bromo-2-chloro/dichloromethylpyrimidines in the similar manner.(Scheme XIII; Table 5.2)
5.3.4 Physical and spectral properties of condensed 4-bromo pyrimidines:

4-Bromo-2-(chloro/dichloromethyl)condensedpyrimidines are yellow crystalline low melting solids. They are freely soluble in most of the organic solvents, except n-hexane. All condensed 4-bromopyrimidines were recrystallised from n-hexane.

IR Spectra:

The IR spectra 4-bromocondensedpyrimidines are devoid of any absorption in the region of 2100 - 2260 cm\(^{-1}\) indicating the absence of C=N. This confirms the participation of cyano group in cyaclocondensation with nitrile.

\(^1\)H NMR Spectra:

The \(^1\)H NMR spectra of 4-bromo-2-chloromethylcondensedpyrimidines exhibited sharp singlet in the region of \(\delta 4.6 - 4.8\) corresponding to two protons of chloromethyl group. 4-bromo-2-dichloromethylcondensedpyrimidine has shown sharp singlet at \(\delta 6.8\) corresponding to one proton of dichloromethyl group. The methylene protons at C-2 were found highly deshielded because of presence of electron withdrawing chloro group.

MASS spectra:

All the synthesised condensed 4-bromopyrimidines 304-308 were also characterised by mass spectra and their mass spectral fragmentation pattern was also studied.

The 4-bromoquinazoline,304, exhibited intense molecular ion peak at 257 and prominant M+2 peak at 259. The loss of Br\(^+\) and Cl\(^-\) from the molecular ion appears to be a major pathway of the decomposition of 304. The cations thus formed can be formulated as 304b and 304e. Low intensity peak observed at m/e 207 in these quinazolines can be attributed to the nitrilium ion 304c. In the lower mass region, bromoquinazoline 304 exhibit an ion peak at m/e 182 which can be assigned to the radical cation 304d, formed by the retro Diels-Alder reaction and loss of CICH2CN from the quinazoline. (Scheme XIV).
4-Bromo-2-chloromethyl-5,6,7,8-tetrahydrothieno(2,3-d)pyrimidine, 307a, is characterised by an intense molecular ion peak at m/e 317, a M+2 peak of about 60% intensity and M+4 peak of about 10% intensity of that of molecular ion. The loss of CH₂=CH₂ by the retro Diels-Alder reaction yields abundant ions of m/e 289, 313. Moderately intense peak at m/e 282 and 241 are due to 309 and 316, respectively. However, contribution by the nitrilium ions 311 and 312 to the intensity of ion peak at m/e 237 and m/e 209, respectively, can not be overlooked. In the lower mass region, the ion peaks observed at m/e 209, 174, and 131 are assigned to the ions 316, 318 and 315 respectively. The ion peaks at m/e 254 and 134 are attributed to the radical cation 317 and 319. The 4-bromo-2-dichloromethylthienopyrimidine 307b exhibits an analogous fragmentation pattern. (Scheme XV)
Scheme XV
The molecular ion of 4-bromo-2-chloromethyl-5,6-dimethylthieno(2,3-d)pyrimidine, 305, shows, in addition to the loss of 'Br and ClCH₂CN, the loss of 'CH₃. Other fragmentation pattern observed are shown in the scheme XVI. Similar fragmentation pattern has been observed with 4-bromo-2-chloromethylfurano-pyrimidines, 306a.
Thus, it appears that under electron impact, the predominant pathway of the decomposition of condensed 4-bromopyrimidines is the loss of nitrile component. The process may be a one step *retro* Diels-Alder reaction (a) or a stepwise bond breaking (b).

A similar process can be envisaged for the loss of BrCN in the spectra of condensed 4-bromopyrimidines.

The condensed pyrimidines possessing a leaving group at the carbon atom attached to second position show a tendency to eliminate the leaving group as a radical and form benzylic type of cation 320. The stability and abundance of these cations may be attributed to their rearrangement to azatropylium species 321.
Decomposition of the azatropylium ion with the loss of HCN yields, generally, the cations of the type 322.
Table 5.1: 4-Bromo-5-carbethoxy-6-(substituted amino)-2-substituted pyrimidines

\[
\text{Br} \\
\begin{array}{c}
\text{H} \\
\text{C}_2\text{O}_2\text{C} \\
\text{HN} \\
\text{N} \\
\text{R}_1 \\
\text{R}_2 \\
\end{array}
\]

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<th>Sr. No.</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>M.P. (°C)</th>
<th>Yield(%)</th>
<th>Mol. Formula</th>
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<td>299a</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;</td>
<td>H</td>
<td>71 - 72</td>
<td>54</td>
<td>C&lt;sub&gt;13&lt;/sub&gt;H&lt;sub&gt;12&lt;/sub&gt;BrN&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;</td>
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<td>299b</td>
<td>p-CH&lt;sub&gt;3&lt;/sub&gt;-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>H</td>
<td>72 - 73</td>
<td>48</td>
<td>C&lt;sub&gt;16&lt;/sub&gt;H&lt;sub&gt;14&lt;/sub&gt;BrN&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;</td>
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<td>299c</td>
<td>o-OCH&lt;sub&gt;3&lt;/sub&gt;-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>H</td>
<td>120-121</td>
<td>61</td>
<td>C&lt;sub&gt;16&lt;/sub&gt;H&lt;sub&gt;14&lt;/sub&gt;BrN&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
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<td>299d</td>
<td>p-chloro-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>H</td>
<td>94 - 96</td>
<td>60</td>
<td>C&lt;sub&gt;13&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;ClBrN&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;</td>
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<td>299e</td>
<td>p-bromo-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>H</td>
<td>98 - 100</td>
<td>56</td>
<td>C&lt;sub&gt;13&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;Br&lt;sub&gt;2&lt;/sub&gt;N&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;</td>
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<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>68 - 69</td>
<td>50</td>
<td>C&lt;sub&gt;16&lt;/sub&gt;H&lt;sub&gt;14&lt;/sub&gt;BrN&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;</td>
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<td>p-CH&lt;sub&gt;3&lt;/sub&gt;-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
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<td>56</td>
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<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
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<td>52</td>
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<td>299i</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;</td>
<td>125 - 126</td>
<td>58</td>
<td>C&lt;sub&gt;16&lt;/sub&gt;H&lt;sub&gt;16&lt;/sub&gt;BrN&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;</td>
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<td>p-CH&lt;sub&gt;3&lt;/sub&gt;-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;</td>
<td>127 - 128</td>
<td>62</td>
<td>C&lt;sub&gt;20&lt;/sub&gt;H&lt;sub&gt;18&lt;/sub&gt;BrN&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;</td>
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<td>o-OCH&lt;sub&gt;3&lt;/sub&gt;-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;</td>
<td>110 - 111</td>
<td>60</td>
<td>C&lt;sub&gt;20&lt;/sub&gt;H&lt;sub&gt;18&lt;/sub&gt;BrN&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
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<td>299l</td>
<td>p-chloro-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;</td>
<td>129 - 131</td>
<td>61</td>
<td>C&lt;sub&gt;16&lt;/sub&gt;H&lt;sub&gt;16&lt;/sub&gt;ClBrN&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;</td>
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* All the compounds were crystallised from n-Hexane
Table 5.2: Condensed 4-bromo-2-chloro/dichloromethylpyrimidines

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<tr>
<th>Sr. No.</th>
<th>R₁</th>
<th>R₂</th>
<th>A</th>
<th>R</th>
<th>X</th>
<th>M.P. (°C)</th>
<th>Yield (%)</th>
<th>Mol. Formula</th>
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<tr>
<td>304</td>
<td>H</td>
<td>H</td>
<td>-CH=CH-</td>
<td>H</td>
<td>Cl</td>
<td>95-97</td>
<td>54</td>
<td>C₉H₆ClBrN₂</td>
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<tr>
<td>305</td>
<td>CH₃</td>
<td>CH₃</td>
<td>S</td>
<td>H</td>
<td>Cl</td>
<td>156-157</td>
<td>30</td>
<td>C₉H₆ClBrN₂S</td>
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<tr>
<td>306a</td>
<td>C₆H₅</td>
<td>C₆H₅</td>
<td>O</td>
<td>H</td>
<td>Cl</td>
<td>118-119</td>
<td>58</td>
<td>C₁₈H₁₂ClBrN₂O</td>
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<tr>
<td>306b</td>
<td>C₆H₅</td>
<td>C₆H₅</td>
<td>O</td>
<td>Cl</td>
<td>Cl</td>
<td>160-161</td>
<td>34</td>
<td>C₁₈H₁₂Cl₂BrN₂O</td>
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<tr>
<td>307a</td>
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<td>S</td>
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<td>Cl</td>
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<tr>
<td>307b</td>
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<td>Cl</td>
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<td>152-154</td>
<td>53</td>
<td>C₁₁H₉Cl₂BrN₂S</td>
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<tr>
<td>308</td>
<td>-C(CH₃)CH=C(CH₃)N-</td>
<td>S</td>
<td>H</td>
<td>Cl</td>
<td>165-166</td>
<td>42</td>
<td>C₁₂H₉ClBrN₂S</td>
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*All the compounds were crystallised from n-Hexane*
5.4 Experimental:

General procedure for the synthesis of N-[2-carbethoxy-2-cyano-1-(arylamino)vinyl]benzamidine.\textsuperscript{367}

To a solution of 0.8g (0.02 mol) of sodium hydroxide in 30ml of ethanol was added, with stirring, 3.9g (0.02 mol) of benzamidine hydrochloride dihydrate. After stirring for 30 minutes, precipitated sodium chloride was filtered off and the filtrate was treated portionwise, with stirring, with 5.3g (0.02 mol) of ethyl 2-cyano-3-(methylthio)-3-(arylamino)acrylate (chapter II) in 15ml of ethanol. The reaction mixture was stirred for 30 minutes and allowed to stand at room temperature for 12 hrs. The mixture was poured into the water. The solid obtained was filtered and dried. Recrystallization from benzene yielded of colourless crystalline product. The m.p. was matched with the reported m.p.

General procedure for the synthesis of N-[2-carbethoxy-2-cyano-1-(arylamino)vinyl]acetamidine.\textsuperscript{367}

To an ice-cold suspension of 1.0g (0.02 mol) of sodium hydride (50%) in 20ml dimethylformamide was added with stirring, 1.9g (0.02 mol) of acetamidine hydrochloride. The mixture was stirred for 30 minutes and treated dropwise, under cooling and stirring, with a solution of 5.3g (0.02 mol) of ethyl 2-cyano-3-(methylthio)-3-(arylamino)acrylate (chapter II) in 15 ml of dimethylformamide. After allowing to stand at room temperature for 12 hrs., the reaction mixture was poured into water. The solid obtained was filtered, washed with water and dried. Recrystallisation from benzene-n-hexane afforded colorless crystalline product. The m.p. was matched with the reported m.p.
Synthesis of 4-bromo-5-carbethoxy-6-{phenylamino}pyrimidine (299a)

To 2.6g (0.01 mol) of N-[2-carbethoxy-2-cyano-1-{phenylamino}vinyl]-formamidine (chapter I), 30ml of dioxane saturated with dry HBr gas was added and stirred at 15-20°C for 2 hrs. Reaction mixture was kept at room temperature for 2 hr. and poured into crushed ice. Solid obtained was filtered, washed with water and dried. Recrystallisation of the crude product from n-hexane yielded 1.7 g (54%) of light yellow coloured product. M.P. 71-72°C. The product was characterized as 4-bromo-5-carbethoxy-6-{phenylamino}pyrimidine, 299a. 

ANALYSIS:

Micro analysis : C_{13}H_{12}BrN_{3}O_{2} 

% Required : C, 48.46 ; H, 3.76 

(322.2) % Found : C, 48.80 ; H, 3.75

IR (KBr) : 3320 (NH), 1695 (C=O), 1610, 1400, 800, 630 cm\(^{-1}\)

UV (CHCl\(_3\)) : 213, 284 nm

\(^1\)H NMR : \(\delta\) 1.33-1.55 (t, 3H, CO\(_2\)CH\(_2\)CH\(_3\)); \(\delta\) 4.30-4.70 

(CDC\(_3\)) : (q, 2H, CO\(_2\)CH\(_3\)CH\(_3\)); \(\delta\) 7.13-7.67 (m, 4H, Ar-H); 

\(\delta\) 8.33 (s, 1H, C-2-pyrim); \(\delta\) 9.70 (s, 1H, NH-Ar)

MASS (m/e) : 324 (M+2), 322 (M+), 276, 248, 222, 168, 141

Synthesis of 4-bromo-5-carbethoxy-6-{(p-methylphenyl)amino}pyrimidine. (299b)

To 2.7g (0.01mol) of N-{2-carbethoxy-2-cyano-1-{(p-methylphenyl)amino}vinyl}formamidine (chapter II), 30ml of dioxane saturated with dry HBr gas was added and stirred for 2 hrs. Reaction mixture was kept at room temperature for 2 hrs. and was further treated according to the procedure described for 299a. Recrystallisation of the crude product from n-hexane yielded 1.6g (48%) of light
yellow coloured product. M.P. 72-73°C. The product was characterized as 4-bromo-5-carbethoxy-6-[(p-methylphenyl)amino]pyrimidine, 299b.

ANALYSIS:

Micro analysis: C₆H₁₄BrN₃O₂
(336.2) % Required: C, 50.01; H, 4.20
% Found: C, 50.40; H, 4.20

IR (KBr): 3260 (NH), 1680 (C=O), 1610, 1390, 630 cm⁻¹

UV (CHCl₃): 207, 285 nm

¹H NMR: δ 1.33-1.52 (t, 3H, CO₂CH₂CH₃); δ 2.36 (s, 3H, (CDCl₃) CH₃arom); δ 4.30-4.70 (q, 2H, CO₂CH₂CH₃); δ 7.13-7.67 (m, 4H, Ar-H); δ 8.33 (s, 1H, C-2pyrim); δ 9.65 (s, 1H, NH-Ar)

MASS (m/e): 338 (M+2), 336 (M+), 290, 262, 235, 198, 183, 155

Synthesis of 4-bromo-5-carbethoxy-6-[(o-methoxyphenyl)amino]pyrimidine (299c).

To 2.9g (0.01 mol) of N-(2-carbethoxy-2-cyano-1[(o-methoxyphenyl)amino]-vinyl]formamidine (chapter II), 30ml of dioxane saturated with dry HBr gas was added and stirred for 2 hrs. Reaction mixture was kept at room temperature for 2 hrs. and was further treated according to the procedure described for 299a. Recrystallisation of the crude product from n-hexane yielded 2.2g (61%) of light yellow coloured product. M.P. 120-121°C. The product was characterized as 4-bromo-5-carbethoxy-6-[(o-methoxyphenyl)amino]pyrimidine, 299c.
**ANALYSIS:**

- Micro analysis: $\text{C}_{14}\text{H}_{14}\text{BrN}_{2}\text{O}_3$ (352.2)
- IR (KBr): 3280 (NH), 1680 (C=O), 1610, 1390, 810, 630 cm$^{-1}$
- UV (CHCl$_3$): 212, 305 nm
- $^1$H NMR: δ 1.40-1.55 (t, 3H, CO$_2$CH$_2$CH$_3$); δ 3.90 (s, 3H, OCH$_3$ arom); δ 4.30-4.35 (q, 2H, CO$_2$CH$_2$CH$_3$); δ 6.82-7.15 (m, 4H, Ar-H); δ 8.35 (s, 1H, C-2$_{pyrm}$); δ 9.80 (s, 1H, NH-Ar)
- MASS (m/e): 354 (M+2), 352 (M+), 321, 306, 278, 251, 199, 171, 129

**Synthesis of 4-bromo-5-carbethoxy-6-[(p-chlorophenyl)amino]pyrimidine (299d).**

To 2.9g (0.01mol) of N-{2-carbethoxy-2-cyano-1[(p-chlorophenyl)amino]-vinyl}formamidine (chapter II), 30ml of dioxane saturated with dry HBr gas was added and stirred for 2 hrs. Reaction mixture was kept at room temperature for 2 hrs. and was further treated according to the procedure described for 299a. Recrystallisation of the crude product from n-hexane yielded 2.1g (60%) of light yellow coloured product. M P 94-96°C. The product was characterized as 4-bromo-5-carbethoxy-6-[(p-chlorophenyl)amino]pyrimidine, 299d.
ANALYSIS:

Micro analysis : C_{13}H_{11}ClBrN_{2}O_{2} % Required : C, 43.78 ; H, 3.11
(356.6) % Found : C, 44.11 ; H, 3.07

IR (KBr) : 3280 (NH), 1680 (C=O), 1610, 1390, 810, 640 cm⁻¹

UV (CHCl₃) : 217, 288nm

¹H NMR : δ 1.40-1.55 (t, 3H, CO₂CH₂CH₃); δ 4.35-4.58 (q, 2H, COCH₃); δ 7.21-7.55 (m, 4H, Ar-H); δ 8.30 (s, 1H, C-2₈pyrim); δ 9.70 (s, 1H, NH-Ar)

Synthesis of 4-bromo-5-carbethoxy-6-[(p-bromophenyl)amino]pyrimidine (299e).
To 3.4g (0.01mol) of N-{2-carbethoxy-2-cyano-1-[(p-bromophenyl)amino]-vinyl}formamidine (chapter II), 30ml of dioxane saturated with dry HBr gas was added and stirred for 2 hrs. Reaction mixture was kept at room temperature for 2 hrs. and was further treated according to the procedure described for 299a. Recrystallisation of the crude product from n-hexane yielded 2.3 g (56%) of light yellow coloured product. M.P. 98-100°C. The product was characterized as 4-bromo-5-carbethoxy-6-[(p-bromophenyl)amino]pyrimidine,299e.

ANALYSIS:
Micro analysis : C_{13}H_{11}Br_{2}N_{2}O_{2} % Required : C, 38.93 ; H, 2.77
(401.1) % Found : C, 39.20 ; H, 2.71
Synthesis of 4-bromo-5-carbethoxy-6-(phenylamino)-2-methylpyrimidine (299f).

To 2.7 g (0.01 mol) of N-[2-carbethoxy-2-cyano-1-(phenylamino)vnyl]-acetamidine, 30 ml of dioxane saturated with dry HBr gas was added and stirred for 2 hrs. Reaction mixture was kept at room temperature for 2 hrs. and was further treated according to the procedure described for 299a. Recrystallisation of the crude product from n-hexane yielded 1.7 g (50%) of light yellow coloured product. M.P. 68-69°C. The product was characterized as 4-bromo-5-carbethoxy-6-(phenylamino)-2-methylpyrimidine, 299f.

ANALYSIS:

Micro analysis: C_{14}H_{14}BrN_{3}O_{2}  
% Required: C 50.01; H < 20  
(336.2)  
% Found: C 50.06; H 4.18

IR (KBr): 3300 (NH), 1670 (C=O), 1600, 1400, 650 cm^{-1}

UV (CHCl_{3}): 214, 278 nm
Synthesis of 4-Bromo-5-carbethoxy-6-[[p-methylphenyl]amino]-2-methyl-pyrimidine (299g).

To 2.9g (0.01mol) of N-{2-carbethoxy-2-cyano-1-[(p-methylphenyl)amino]-vinyl}acetamidine, 30ml of dioxane saturated with dry HBr gas was added and stirred for 2 hrs. Reaction mixture was kept at room temperature for 2 hrs. and was further treated according to the procedure described for 299a. Recrystallisation of the crude product from n-hexane yielded 2.0g (56%) of light yellow coloured product. M.P. 70-71°C. The product was characterized as 4-bromo-5-carbethoxy-6-[[p-methylphenyl]amino]-2-methylpyrimidine.299g.

ANALYSIS:

Micro analysis : C_{15}H_{16}BrN_{3}O_{2} % Required: C.51.44 ; H.4.61
(350.2) % Found : C.51.38 ; H.4.50

IR (KBr) : 3250 (NH), 1670 (C=O), 1605, 1410, 650 cm⁻¹

UV (CHCl₃) : 212, 287nm

¹H NMR : δ 1.38-1.53 (t, 3H, CO₂CH₂CH₃), δ 2.35 (s, 3H, CH₃pyrmn);
(CDCl₃) δ 2.52 (s, 3H, CH₃pyrmn), δ 4.32-4.55 (q,2H, CO₂CH₂CH₃).
δ 7.35-7.50 (m,4H,Ar-H), δ 9.65 (s, 1H, NH-Ar)

MASS (m/e) : 352 (M+2), 350 (M+), 304, 276, 235, 196, 224, 183, 155
Synthesis of 4-bromo-5-carbethoxy-6-[(p-methoxyphenyl)amino]-2-methylpyrimidine (299h).

To 3.0g (0.01mol) of N-{2-carbethoxy-2-cyano-1[(p-methoxyphenyl)amino]-vinyl}acetamidine, 30ml of dioxane saturated with dry HBr gas was added and stirred for 2 hrs. Reaction mixture was kept at room temperature for 2 hours and was further treated according to the procedure described for 299a. Recrystallisation of the crude product from n-hexane yielded 1.9g (52%) of light yellow coloured product. M.P.72-74°C. The product was characterized as 4-bromo-5-carbethoxy-6-[(p-methoxyphenyl)amino]-2-methylpyrimidine, 299h.

ANALYSIS:

Micro analysis: C_{15}H_{16}BrN_{3}O_{3} (366.2)

% Required : C, 49.19; H, 4.40
% Found : C, 49.57; H, 4.59

IR (KBr) : 3260 (NH), 1670 (C=O), 1605, 1410, 645 cm^{-1}

UV (CHCl_{3}) : 215, 289nm

^{1}H NMR : \delta 1.38-1.53 (t, 3H, CO_{2}CH_{2}CH_{3}); \delta 2.50 (s, 3H, CH_{3}aron); \delta 3.80 (s, 3H, CH_{3}pyrim); \delta 4.32-4.55 (q, 2H, CO_{2}CH_{2}CH_{3}); \delta 7.10-7.55 (m, 4H, Ar-H); \delta 9.68 (s, 1H, NH-Ar)

MASS (m/e) : 368 (M+2), 366 (M+), 320, 292, 286, 279, 251, 245, 217, 212
Synthesis of 4-bromo-5-carbethoxy-6-(phenylamino)-2-phenylpyrimidine (299i).

To 3.3g (0.01 mol) of N-[2-carbethoxy-2-cyano-1-(phenylamino)vinyl]-benzamidine, 30ml of dioxane saturated with dry HBr gas was added and stirred for 2 hrs. Reaction mixture was kept at room temperature for 2 hours and was further treated according to the procedure described for 299a. Recrystallisation of the crude product from n-hexane yielded 2.3g (58%) of light yellow coloured product. M.P. 125-126°C. The product was characterized as 4-bromo-5-carbethoxy-6-(phenylamino)-2-phenylpyrimidine, 299i.

ANALYSIS:

Micro analysis : C_{19}H_{16}BrN_{3}O_{2} (398.3) % Required : C, 57.30 ; H, 4.05 % Found : C, 56.98 ; H, 3.80

IR (KBr) : 3260 (NH), 3000, 1680 (C=O), 1610, 1410, 670 cm\(^{-1}\)

UV (CHCl\(_3\)) : 216, 285nm

\(^1\)H NMR (CDCl\(_3\)) : δ 1.4-1.58 (t, 3H, CO\(_2\)CH\(_2\)CH\(_3\)\), δ 4.34-4.58 (q, 2H, CO\(_2\)CH\(_2\)CH\(_3\)); δ 7.20-7.70 (m, 10H, Ar-H); δ 9.85 (s, 1H, NH-Ar)

MASS (m/e) : 400 (M+2), 398 (M+), 352, 324, 272, 249, 244, 221, 169, 141
Synthesis of 4-Bromo-5-carbethoxy-6-[(p-methylphenyl)amino]-2-phenyl-pyrimidine (299j).

To 3.5g (0.01 mol) of N-{2-carbethoxy-2-cyano-1-[(p-methylphenyl)amino]vinyl}benzamidine, 30ml of dioxane saturated with dry HBr gas was added and stirred for 2 hrs. Reaction mixture was kept at room temperature for 2 hours and was further treated according to the procedure described for 299a. Recrystallization of the crude product from n-hexane yielded 2.6 g (62%) of light yellow coloured product. M.P 127-128°C. The product was characterized as 4-bromo-5-carbethoxy-6-[(p-methylphenyl)amino]-2-phenylpyrimidine,299j.

ANALYSIS:

Micro analysis : C20H18BrN3O2 (412.3) % Required: C,58.26 ; H,4.40 % Found : C,58.65 ; H,4.39

IR (KBr) : 3280 (NH), 3000, 1680 (C=O), 1600, 1410, 670 cm⁻¹

UV(CHCl₃ ) : 213, 286nm

¹H NMR : δ 1.3-1.46(t, 3H, CO₂CH₂CH₃); δ 2.30 (s, 3H, CH₃ arom);
(CDCl₃) δ 4.34-4.58 (q,2H, CO₂CH₂CH₃); δ 7.20-7.70 (m, 10H, Ar-H); δ 9.85(s, 1H, NH-Ar)

MASS (m/e) : 414 (M+2), 412 (M+), 364, 336, 256, 284, 232, 204, 153, 125

Synthesis of 4-bromo-5-carbethoxy-6-[(o-methoxyphenyl)amino]-2-phenyl-pyrimidine (299k).

To 3.6g (0.01 mol) of N-{2-carbethoxy-2-cyano-1-[(o-methoxyphenyl)amino]vinyl}benzamidine, 30ml of dioxane saturated with dry HBr gas was added and stirred for 2 hrs. Reaction mixture was kept at room temperature for 2 hrs. and was further treated according to the procedure described for 299a.
Recrystallisation of the crude product from n-hexane yielded 2.6g (60%) of light yellow coloured product. M.P. 110 - 111°C. The product was characterized as 4-bromo-5-carbethoxy-6-[(o-methoxyphenyl)amino]-2-phenylpyrimidine.299k.

**ANALYSIS:**

**Micro analysis :** C_{20}H_{18}BrN_{3}O_{3}  
(428.3)  
% Required : C, 56.08; H, 4.24  
% Found : C, 56.21; H, 4.18

**IR (KBr) :** 3240 (NH), 2990, 1680 (C=O), 1600, 1410, 670 cm^{-1}

**UV (CHCl₃) :** 216, 282nm

**¹H NMR :** δ 1.4-1.56 (t, 3H, CO₂CH₂CH₃); δ 3.90 (s, 3H, OCH₃); δ 4.35-4.60 (q, 2H, CO₂CH₂CH₃); δ 6.90-7.48 (m, 10H, Ar-H); δ 9.90 (s, 1H, NH-Ar)

**MASS (m/e) :** 430 (M+2), 428 (M+), 398, 382, 354, 350, 308, 199, 165, 120

**Synthesis of 4-bromo-5-carbethoxy-6-[(p-chlorophenyl)amino]-2-phenylpyridimidine (299l).**

To 3.7g (0.01mol) of N-[2-carbethoxy-2-cyano-1-[(p-chlorophenyl)amino]vinyl]benzamidine, 30ml of dioxane saturated with dry HBr gas was added and stirred for 2 hrs. Reaction mixture was kept at room temperature for 2 hrs. and was further treated according to the procedure described for 299a. Recrystallisation of the crude product from n-hexane yielded 2.6g (61%) of light yellow coloured product. M.P. 129-131°C. The product was characterized as 4-bromo-5-carbethoxy-6-[(p-chlorophenyl)amino]-2-phenylpyrimidine.299l.
ANALYSIS:

Micro analysis: C₁₉H₁₅ClBrN₃O₂  (432.7)
% Required: C, 52.73; H, 3.49
% Found: C, 52.43; H, 3.48

IR (KBr): 3280 (NH), 3000, 1680 (C=O), 1620, 1400, 670 cm⁻¹

UV (CHCl₃): 214, 288 nm

¹H NMR: δ 1.4-1.56 (t, 3H, CO₂CH₂CH₃); δ 4.32-4.50 (q, 2H, CO₂CH₂CH₃); δ 7.20-7.60 (m, 10H, Ar-H); δ 9.92 (s, 1H, NH-Ar)

MASS (m/e): 434 (M+2), 432 (M+), 386, 358, 306, 278, 256, 221, 203, 175, 111

Synthesis of 4-bromo-2-chloromethylquinazoline (304).

To a mixture of 1.2 g (0.01 mol) of 2-aminobenzonitrile and 0.8 g (0.011 mol) of chloroacetonitrile was added, 30 ml of dioxane saturated with dry HBr gas and stirred for 2 hrs. The reaction mixture was kept at room temperature for 2 hours and poured into crushed ice. Solid obtained was filtered, washed thoroughly with water and dried. Recrystallisation of the crude product with n-hexane yielded 1.4 g (54%) of pale yellow coloured product, M.P. 95-97°C. The product was characterized as 4-bromo-2-chloromethylquinazoline, 304.

ANALYSIS:

Micro analysis: C₉H₆ClBrN₂  (257.5)
% Required: C, 41.97; H, 2.35; N, 10.88
% Found: C, 42.32; H, 2.54; N, 10.52

IR (KBr): 3040, 2980, 1610, 1560, 810, 760 cm⁻¹

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Synthesis of 4-bromo-2-chloromethyl-5,6-dimethylthieno(2,3-d)pyrimidine (305).

2-Amino-3-cyano-4,5-dimethylthiophene\textsuperscript{375} 1.2 g (0.01 mol) was reacted with 0.8 g (0.011 mol) of chloroacetonitrile in 30 ml of dioxane saturated with dry HB\textsuperscript{-} gas according to the procedure described for 304. The solid obtained, on pouring the reaction mixture into ice, was filtered, washed with water and dried. Recrystallisation from n-hexane yielded 0.9 g (30\%) of pale yellow coloured product. M.P. 156-157\degree C. The product was characterized as 4-bromo-2-chloromethyl-5,6-dimethylthieno(2,3-d)pyrimidine,\textsuperscript{305}.

**ANALYSIS:**

- **Micro analysis:** C\textsubscript{9}H\textsubscript{8}ClBrN\textsubscript{2}S  
  \% Required: C,37.07 H,2.77 N,9.60  
  \% Found: C,36.68 H,2.76 N,9.33  

- **IR (KBr):** 3040, 2980, 1550, 1400, 810, 660 cm\textsuperscript{-1}

- **\textsuperscript{1}H NMR:** δ 2.55 (s, 6H, \textsuperscript{5}C-CH\textsubscript{3} & \textsuperscript{6}C-CH\textsubscript{3}), δ 4.6 (s, 2H, CH\textsubscript{2}Cl)  

- **MASS (m/e):** 293 (M+2), 291 (M+), 276, 256, 215, 211, 170, 135, 123
Synthesis of 4-bromo-2-chloromethyl-5,6-diphenylfurano(2,3-d)pyrimidine (306a).

2-Amino-3-cyano-4,5-diphenylfuran\textsuperscript{376} 2.6g (0.01 mol) was reacted with 0.8g (0.011 mol) of chloroacetonitrile in 30ml of dioxane saturated with dry HBr gas according to the procedure described for 304. The solid obtained, on pouring the reaction mixture into ice, was filtered, washed with water and dried. Recrystallisation from n-hexane yielded 2.3 g (58 \%) of pale yellow coloured product, M.P. 118-119°C. The product was characterized as 4-bromo-2-chloromethyl-5,6-diphenylfurano(2,3-d)pyrimidine, 306a.

ANALYSIS:

Micro analysis: C\textsubscript{19}H\textsubscript{12}ClBrN\textsubscript{2}O

\begin{align*}
\text{% Required:} & \quad C, 57.09 \quad H, 3.03 \quad N, 7.00 \\
\text{% Found:} & \quad C, 57.45 \quad H, 3.40 \quad N, 7.43 \\
\end{align*}

IR (KBr) : 3050, 2980, 1600, 1550, 1380, 645 cm\textsuperscript{-1}

\textsuperscript{1}H NMR : \delta 4.7 (s, 2H, CH\textsubscript{2}Cl), \delta 7.3 - 7.6 (m, 10H\textsubscript{arom})

(CDC\textsubscript{3})

MASS (m/e) : 402(M+2), 400(M+), 364, 320, 324, 323, 217, 189

Synthesis of 4-bromo-2-dichloromethyl-5,6-diphenylfurano(2,3-d)pyrimidine (306b).

2-Amino-3-cyano-4,5-diphenylfuran\textsuperscript{377} 2.6g (0.01 mol) was reacted with 1.2g (0.011 mol) of dichloroacetonitrile in 30ml of dioxane saturated with dry HBr gas according to the procedure described for 304. The solid obtained, on pouring the reaction mixture into ice, was filtered, washed with water and dried. Recrystallisation from n-hexane yielded 1.5g (34 \%) of pale yellow coloured product, M.P. 160-161°C. The product was characterized as 4-bromo-2-dichloromethyl-5,6-diphenylfurano(2,3-d)pyrimidine, 306b.
Synthesis of 4-bromo-2-chloromethyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)-pyrimidine (307a).

2-Amino-3-cyano-4,5,6,7-tetrahydrobenzo(b)thiophene was reacted with 0.8g (0.011 mol) of chloroacetonitrile in 30ml of dioxane saturated with dry HBr gas according to the procedure described for 304. The solid obtained, on pouring the reaction mixture into ice, was filtered, washed with water and dried. Recrystallisation from n-hexane yielded 1.4g (44%) of pale yellow coloured product, M.P. 136-138°C. The product was characterized as 4-bromo-2-chloromethyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidine, 307a.

ANALYSIS:

Micro analysis : C_{19}H_{11}ClBrN_{2}S % Required: C,41.60 H,3.17 N,8.82 (317.6) % Found : C,42.07 H,2.93 N,8.55

IR (KBr) : 3040, 2960, 1560, 1480, 810, 660 cm\(^{-1}\)

\(^1\)H NMR : δ 1.9 - 2.2 (m, 8H, -(CH\(_2\))\(_4\)); δ 4.65 (s, 2H, CH\(_2\)Cl) (CDCl\(_3\))
Synthesis of 4-bromo-2-dichloromethyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)-pyrimidine (307b).

2-Amino-3-cyano-4,5,6,7-tetrahydrobenzo(b)thiophene \(^{375}\) 1.8g (0.01 mol) was reacted with 1.2g (0.011 mol) of dichloroacetonitrile in 30ml of dioxane saturated with dry HBr gas, according to the procedure described for 304. The solid obtained, on pouring the reaction mixture into ice, was filtered, washed with water and dried. Recrystallisation from n-hexane yielded 1.1g (53%) of pale yellow coloured product, M.P. 152-154°C. The product was characterized as 4-bromo-2-dichloromethyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidine, 307b.

ANALYSIS:

Micro analysis: \( \text{C}_{11}\text{H}_9\text{Cl}_2\text{BrN}_2\text{S} \) % Required: C, 37.52 H, 2.59 N, 7.96 \((352.1)\) % Found: C, 38.12 H, 2.69 N, 8.13

IR (KBr) : 3020, 2970, 1560, 1480, 810, 650 cm\(^{-1}\)

\(^{1}\text{H NMR}\) (CDCl\(_3\)): \( \delta 1.8 - 2.2 \) (m, 8H, \(-\text{CH}_2\) \(\text{Br}\)); \( \delta 6.80 \) (s, 2H, \(\text{CH}_2\text{Cl}_2\))

MASS (m/e): \(354 \text{ (M+2)}, 352 \text{ (M+)}, 324, 316, 289, 272, 244, 241, 223, 208, 166\)

3-Amino-2-cyano-4,6-dimethylthieno(2,3-b)pyridine 2.0g (0.01 mol) was reacted with 0.8g (0.011 mol) of chloroacetonitrile in 30ml of dioxane, saturated with dry HBr gas, according to the procedure described for 304. The solid obtained, on pouring the reaction mixture into ice-water, was filtered, washed with water and dried. Recrystallisation from n-hexane yielded 1.4g (42%) of pale yellow coloured product, M.P. 165-166°C. The product was characterized as 4-bromo-2-chloromethyl-7,9-dimethylpyrido[3',2':4,5]thieno(3,2-d)pyrimidine,308.

ANALYSIS:

Micro analysis: C_{12}H_{9}ClBrN_{3}S   % Required: C, 42.06  H, 2.65
(342.6)   % Found : C, 42.20  H, 2.44

IR (KBr) : 3040, 1550, 1490, 1380, 790, 640 cm^{-1}

^1^H NMR : δ 1.8 - 2.2 (m, 8H, -(CH_{2})_{4}); δ 6.80 (s, 2H, CH_{2}Cl)
(CDC_{6})

MASS (m/e) : 344 (M+2), 342 (M+), 327, 312, 266, 262, 211, 135