CHAPTER - 1

GENERAL INTRODUCTION

1.1 Thieno[2,3-b]pyridines

Thienopyridines are bi-heterocycles in which a $\pi$-excessive thiophene ring is fused to a $\pi$-deficient pyridine nucleus. The six possible thienopyridines have been found in literature. Thienopyridines have been divided into two groups. Those that are analogous to quinoline the \([x,y-b]\) fused system (1-3) and those that are analogous to isoquinoline the \([x,y-c]\) fused system (4-6) ($X = Y = 2,3,4$).

\[
\begin{align*}
1 & \quad \text{[2,3-b]} \\
2 & \quad \text{[3,2-b]} \\
3 & \quad \text{[3,4-b]} \\
4 & \quad \text{[2,3-c]} \\
5 & \quad \text{[3,2-c]} \\
6 & \quad \text{[3,4-c]} \\
\end{align*}
\]

From amongst all the six thienopyridines (1-6), our interest lies in thieno[2,3-b]-pyridines (1).\textsuperscript{10}

Synthesis of thieno[2,3-b]pyridines has been considered under two headings according to which heterocyclic ring is constructed.
1.1.1 Synthesis involving formation of pyridine ring
1.1.2 Synthesis involving formation of thiophene ring

1.1.1 Synthesis involving formation of pyridine ring

(1) Skraup Synthesis

Steinkopf\textsuperscript{1, 2} prepared thienopyridine for the first time by applying the Skraup synthesis, according to which $(\text{C}_4\text{H}_3\text{S-NH}_3)_2\text{SnCl}_6^{2-}$ (7) obtained directly by reduction of 2-nitrothiophene to prepare thieno[2,3-b]pyridine in low yield. Russian workers\textsuperscript{3} reported the reaction between methylvinyl ketone and 2-aminothiophene double salt in order to get 4-methylthieno[2,3-b]pyridine (8) Klemm\textsuperscript{4} showed that a minor amount of the 6-methyl isomer (9) was also produced during this process (Scheme-1).

\begin{center}
\begin{tikzpicture}
\node at (0,0) {7};
\node at (2,1) {O\textsubscript{CO}C\textsubscript{CH}};
\node at (4,0) {CH\textsubscript{3}};
\node at (4,1) {CH\textsubscript{3}};
\node at (5,0) {H\textsubscript{3}C};
\node at (5,1) {N\textsubscript{H\textsubscript{2}}} ds;
\node at (8,1) {H\textsubscript{3}C};
\node at (8,0) {N\textsubscript{H\textsubscript{2}}} ds;
\node at (10,0) {CH\textsubscript{2}};
\node at (10,1) {N\textsubscript{H\textsubscript{2}}} ds;
\node at (12,1) {H\textsubscript{3}C};
\node at (12,0) {N\textsubscript{H\textsubscript{2}}} ds;
\end{tikzpicture}
\end{center}

\begin{center} Scheme 1 \end{center}

2,3,4-Trimethylthieno[2,3-b]pyridine\textsuperscript{5} (11) was obtained by condensation reaction of 4,5-dimethyl-2-aminothiophene (10) with methyl vinyl ketone (Scheme-2).

\begin{center}
\begin{tikzpicture}
\node at (0,0) {10};
\node at (2,1) {O\textsubscript{CO}C\textsubscript{CH}};
\node at (4,0) {CH\textsubscript{3}};
\node at (4,1) {CH\textsubscript{3}};
\node at (5,0) {C\textsubscript{2}H\textsubscript{5}OH};
\node at (7,0) {C\textsubscript{2}H\textsubscript{5}OH};
\node at (8,0) {FeCl\textsubscript{3}/ ZnCl\textsubscript{2}};
\node at (10,1) {H\textsubscript{3}C};
\node at (10,0) {N\textsubscript{H\textsubscript{2}}} ds;
\node at (12,1) {H\textsubscript{3}C};
\node at (12,0) {N\textsubscript{H\textsubscript{2}}} ds;
\node at (14,1) {H\textsubscript{3}C};
\node at (14,0) {N\textsubscript{H\textsubscript{2}}} ds;
\node at (16,1) {H\textsubscript{3}C};
\node at (16,0) {N\textsubscript{H\textsubscript{2}}} ds;
\node at (18,1) {H\textsubscript{3}C};
\node at (18,0) {N\textsubscript{H\textsubscript{2}}} ds;
\end{tikzpicture}
\end{center}

\begin{center} Scheme 2 \end{center}

(43 %)
(ii) Reaction of aminothiophenes with 1,3-dicarbonyl compounds

The first application of this approach was reported by Emarson, Holly and Klemm. 2-Aminothiophene double salt (7) was treated with acetylacetone to give Schiff's base (12) which on cyclization gave 4,6-dimethylthieno[2,3-b]pyridine (13) in excellent yield (Scheme-3).

\[ \text{Scheme 3} \]

The acetal and ketals of 1,3-dicarbonyl compounds were found to be effective in the synthesis of thienopyridine.

Thieno[2,3-b]pyridine (1) was prepared by cyclocondensation of 2-aminothiophene double salt (7) with malondialdehyde tetraethyl acetal MTA (14) (Scheme-4).

\[ \text{Scheme 4} \]

The acetal and ketals of 1,3-dicarbonyl compounds were found to be effective in the synthesis of thienopyridine.
Klemm showed that presence of deactivating group on the thiophene ring does not prevent cyclization (Scheme-5).

\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{COCH}_3 \\
\text{15} & \quad \text{1. NO}_2 \rightarrow \text{NH}_2 \\
\text{2. MTA} & \quad \text{ZnCl}_2/\text{C}_2\text{H}_5\text{OH} \\
\text{16} & \quad \text{Scheme 5}
\end{align*}
\]

Zhiryakov and Abramenko claimed that the reaction of the diethylacetal / ketal of 3-ketobutanal with 2-aminothiophene double salt (7) led to 6-methylthieno[2,3-b]pyridine (9). The diethylacetal (17) of this dicarbonyl compound, however was shown to yield mainly 5-acetylthieno[2,3-b]pyridine (18), only minor amount of 4/6-methylthieno[2,3-b]pyridine (8 and 9) being formed (Scheme-6).

\[
\begin{align*}
\text{7} & \quad \text{CH}_3\text{COCH}_2\text{CH (OC}_2\text{H}_5)_2 \\
\rightarrow & \quad \text{17} \\
\text{18} & \quad \text{(32 \%)} \\
\text{8} & \quad \text{9} \quad \text{(2-5 \%)}
\end{align*}
\]

\[
\text{Scheme 6}
\]

2-Aminothiophene (19) with 2-nitropropane-1,3-dial [OCH-CH(NO₂)CHO] gave 2,3-disubstituted 5-nitrothieno[2,3-b]pyridines (21) via intermediate (20) (Scheme-7).
4-Amino-5-cyanothieno[2,3-b]pyridine (23) and 4-acylaminothieno[2,3-b]pyridine (24) were prepared by condensation of 2-amino-3-cyanothiophene (22) with ethoxymethylene malononitrile (EMMN) and β-diketones respectively followed by cyclization with AlCl₃ (Scheme 8).

\[
\begin{align*}
\text{EMMN} & \quad \rightarrow \\
\begin{array}{c}
\text{N} \\
\text{C} \\
\text{C} \\
\text{C} \\
\end{array} & \quad \rightarrow \\
\begin{array}{c}
\text{N} \\
\text{H} \\
\text{C} \\
\text{C} \\
\end{array}
\end{align*}
\]

R=H; R₁=R₂= CH₃, C₆H₅; R₁R₂= C(CH₂)₄, CH=CH=CH=CH

Scheme 8
Cyclocondensation of 2-amino-3-cyanothiophene (22) with ethyl cyanoacetate and ethyl-3-cyanoamino crotonate in presence of sodium ethoxide yielded 4-amino-5-cyanothieno[2,3-b]pyridinones\textsuperscript{9,10} (25) and 4-amino-6-methylthieno[2,3-b]pyridine-5-carboxylic acid\textsuperscript{11} (26) respectively (Scheme-9).

\[ \begin{align*}
\text{22} & \xrightarrow{a} \text{25} \\
\text{a} = \text{Ethylcyano acetate}; \text{b} = \text{Ethyl-3-cyanoamino crotonate} \\
R = \text{H}; R_1 = \text{CH}_3, \text{C}_6\text{H}_5; RR_1 = (\text{CH}_2)_4, \text{CH}_3\text{CHCH}_2\text{CH}
\end{align*} \]

Scheme 9

2-Aminothiophene double salt (7) and 2-aminothiophene derivatives (27) have been condensed with ethoxymethylene derivatives of active methylene compounds (28) to afford intermediate (29) which subsequently cyclized to give thieno[2,3-b]pyridine-4(1H)-ones (30)\textsuperscript{12,13,14} (Scheme-10).
2,3,5-Trisubstituted 4-hydroxythieno[2,3-b]pyridine (32)\textsuperscript{15} was synthesized by the ring closure of 4,5-disubstituted thiophene-3-carboxylic acid (31) (Scheme-11).

\begin{align*}
\text{Scheme 10}
\end{align*}

(iii) Cyclization of O-aminocarbonylthiophene

Raich and Hamilton\textsuperscript{16} prepared 6-phenythieno[2,3-b]pyridine (36) by using 3-methylthiophene (33) (Scheme-12). Here, difficulty lies in the preparation of appropriately substituted thiophene.
Shvedov et al.\textsuperscript{17,18} carried out Vilsmeier reaction on various 4,5-disubstituted 2-acylthienyl amines (37) and cyclized the resulting 3-formyl derivatives (38) with a variety of active methylene compound to get thieno[2,3-b]pyridine (39) (Scheme-13).

Similarly, 2-acetamidothiophenes (40) have been cyclized in one step by DMF / \textsubscript{POCl}_3 mixture in varying proportion to obtain a mixture of 6-chlorothieno[2,3-b]pyridine (41) and 5-formyl-6-chlorothieno[2,3-b]pyridine (42)\textsuperscript{19,20} (Scheme-14).
2,3,4-Trisubstituted tetrahydrobenzothieno[2,3-b]pyridine\(^{21}\) (44) was synthesized by the reaction of 3-benzoyl-2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene (43) and 1,1-dimethylthio-2-nitroethylene (Scheme-15).

Reaction of 2-acetamidothiophene-3-ethoxylate (45) with \([(CH_3)_2N]_3PO\) gave 4,6-bis(dimethylamino)thieno[2,3-b]pyridine (46)\(^{22}\) (Scheme-16).
methyl-2-phenylthieno[2,3-b]pyridine (52). The latter compound was stirred with 2,6-difluorobenzyl bromide to give N-substituted thieno[2,3-b]pyridine (53) (Scheme-19).

![Scheme 19](image)

1.1.2 Synthesis involving formation of thiophene ring

Chichibabin and Vorozhto prepared methyl-3-hydroxythieno[2,3-b]pyridine-2-carboxylate (55) from methyl-2-chloropyridine-3-carboxylate (54) (Scheme-20).

![Scheme 20](image)
3-Hydroxy-6-methylthieno[2,3-b]pyridine (57) was synthesized by the reaction of 3-carboxyl-6-methyl-2-pyridine thioacetic acid (56) with acetic anhydride (Scheme-21).

![Scheme 21](image)

The synthesis of novel 4,7-thieno[2,3-b]pyridines (59) was accomplished by refluxing o-chloroformyl substituted 1,4-dihydropyridine (58) in the presence of sodium ethoxide and dry ethanol under an inert atmosphere (Scheme-22).

![Scheme 22](image)

(i) **Cyclization of cyanopyridyl thioacetic acid derivatives**

The reaction of 2-chloropyridine-3-carbonitriles (60) with thioacetic acid derivatives (HSCH$_2$X) in presence of sodium carbonate$^{28}$ or sodium alkoxide$^{29}$ solution, yielded 3-aminothieno[2,3-b]pyridine derivatives (61) (Scheme-23).
where, X = CO$_2$H, CO$_2$CH$_3$, CO$_2$C$_2$H$_5$, COCO$_2$CH$_3$, CONH$_2$, CONHPh;
R = H, CH$_3$; R$_t$ = H, NO$_2$; R$_r$ = H, CH$_3$, C$_2$H$_5$, CO$_2$C$_2$H$_5$

Scheme 23

Dave et al$^{30}$ showed Thorpe-Ziegler type of cyclization. 2-Carbethoxy-3-
aminothieno[2,3-b]pyridine (64) was synthesized from the reaction of 2-chloro-3-cyano pyridine (62) and ethyl thioglycolate. The intermediate (63) was isolated in this method, and then cyclized using sodium ethoxide (Scheme-24).

Scheme 24

3-Aminothieno[2,3-b]pyridine (66)$^{31}$ was prepared from 2-chloro-3-cyanopyridine (65) (Scheme-25).
(ii) From 3-cyanopyridine-2(1H)-thiones and halo acetic acid derivatives

3-Aminothieno[2,3-b]pyridines (69) have been prepared \(^{32-44,45-47}\) by the alkylation of 3-cyanopyridine-2(1H)-thiones (67) with halo acetic acid derivatives (XCH₂Y) and subsequent cyclization of the intermediate methylmercaptopyridines (68). The intermediate (68) have not been isolated in almost all the cases\(^{39-43}\) (Scheme-26).

5,6-Disubstituted 3-aminothieno[2,3-b]pyridine (72)\(^{48}\) were prepared by reaction of 3-cyanopyrido-2(1H)-thiones (70) with haloalkane derivatives (Scheme-27).
5-Substituted 6-amino-4-aryl-3-cyanopyridine-2(1H)-thiones (73) were reacted with haloalkanes to give intermediates (74), which were then cyclized to give 2,5-disubstituted 3,6-diamino-4-arylthieno[2,3-b]pyridines 49,50,51 (75) (Scheme-28).

3,5-Dicyano-6-mercapto-4-phenylpyridine-2(1H)-ones52,53 (76) were treated with ClCH₂CN and NaOAC in absolute alcohol to give intermediates (77) which cyclized in the presence of NaOC₂H₅ to give thieno[2,3-b]pyridines (78) (Scheme-29).
4-Aryl-5-methyl-3-cyano-2(1H)-pyridinethiones (79) was reacted with chloro acetonitrile to give S-alkylated derivative which upon treatment with NaOEt in EtOH give 2-cyano-3-amino-4-aryl-6-methylthieno[2,3-b]pyridine (80)\textsuperscript{54} (Scheme-30).

Kaigorodova et al\textsuperscript{55} showed that 2-substituted 6-methoxymethyl-4-methyl-3-cyanopyridine (82) was prepared by the nucleophilic substitution of chlorine atoms of 2-chloro-3-cyano-6-methoxymethyl-4-methylpyridine (81) by mercapto group, compound 82 was then treated with sodium ethoxide to give 2-substituted 3-amino-6-methoxymethyl-4-methylthieno[2,3-b]pyridine (83) (Scheme-31).
3-Cyanopyridine-2(1H)-thiones (84) was reacted with bromo nitromethane in presence of triethylamine to give 3-amino-2-nitrothieno[2,3-b]pyridines (85)\(^{56}\) (Scheme-32).

\[ R = CH_2CO_2H, CH_2CO_2C_2H_5; X = CO_2H, CO_2C_2H_5, CONH_2 \]

Scheme 31

4,6-Disubstituted 3-amino-2-carbethoxythieno[2,3-b]pyridine (87) \(^{57}\) was prepared by reacting 4,6-disubstituted 3-cyanopyridine-2-thiones (86) with ethyl chloroacetate and Sodium ethoxide (Scheme-33).
Similarly, 5-substituted 3-amino-2-carbethoxy-4,6-dimethylthieno[2,3-b]pyridine\textsuperscript{52-58} (89) was synthesized by reacting 5-substituted 3-cyano-4,6-dimethylpyridine-2-thione (88) with ethyl chloroacetate and DMF (Scheme-34).

2-Substituted 4-methylmercapto-3,6-diamino-5-cyanothieno[2,3-b]pyridines (91)\textsuperscript{59} have been synthesized by cyclocondensation of 3,5-dicyano-4-methylmercapto-6-aminopyridine-2-thione (90) with XCH\textsubscript{2}R\textsuperscript{1} which was further refluxed with pyridine, triethylamine and PhCOCH\textsubscript{2}Cl to give thienopyridine (Scheme-35).
3-Cyano-6-methyl-4-(5-methyl-2-furyl)pyridine-2(1H)-thiones (92)\textsuperscript{60} was reacted with α-chloro acetamide to give S-alkylated product (93) which was cyclized to thieno[2,3-b]pyridine (94) (Scheme-36).

Samioshkin\textsuperscript{61} showed that intramolecular cyclization of 2-(o-carboran-1-yl)methylthio-3-cyanopyridines (95)\textsuperscript{95} under the influence of KOH / DMF gives corresponding thieno[2,3-b]pyridine (96) (Scheme-37).
3-Cyano-5-(phenylazo)-4,6-dimethylpyridine-2-thiones (97) was reacted with halo compound to give S-alkylated derivative, which upon treatment with NaOEt in EtOH give 2-substituted 3-amino-5-(phenylazo)-4,6-dimethylthieno[2,3-b]pyridine (98) (Scheme-38).

\[
\begin{align*}
\text{95} & \quad \xrightarrow{\text{DMF, KOH}} \quad \text{96} \\
X = \text{(O-carboran-1-yl)}
\end{align*}
\]

Scheme 37

(iii) **High temperature catalytic cyclization**:

A mixture of thieno[2,3-b]pyridine (1) and thieno[3,2-c]pyridine (5) was obtained by the reaction of 3-vinyl (99) or 3-ethylpyridine (100) and hydrogen sulfide over iron (II) sulfide alumina catalyst at 630 °C (Scheme-39).
2,3-Dihydro-2,2-diphenylthieno[2,3-b]pyridine (102) was prepared from 3-methylpyridine-2(1H)-thione (101) (Scheme-40).

Taylor synthesized 2,3-dihydrothieno[2,3-b]pyridine (104) through intramolecular Diels-Alder reaction with alkylthio derivatives of 1,2,4-triazines (103) (Scheme-41).
Ethyl-7-ethyl-2-formyl-4,7-dihydro-4-oxothieno[2,3-b]pyridine-5-carboxylate (106) was obtained from diethyl[ethyl-(5-formyl-2-thienyl)amino)methylene]malonate (105) (Scheme-42).

2-Substituted 3,4-diamino-5-cyano-6-methylmercaptothieno[2,3-b]pyridine (108) was prepared under phase transfer condition starting with 3,5-dicyano-4-amino-6-methylmercaptopyridin-2-thione (107) and halo compound XCH2R (Scheme-43).
1.2 Reactions of thieno[2,3-b]pyridines

Electrophilic substitution

The first attempted electrophilic substitution in thienopyridine was prepared by Sheehan and Leifner,\textsuperscript{67} who found out that treatment of 3-hydroxythieno[3,2-c]pyridines (109) with iodine monochloride (ICl) gave a yellow moniodo derivative in which the iodine atom was very labile. The structure of the product was not established, it seems perhaps that it was 3-hydroxy-2-iodothieno[3,2-c]pyridine (110), the lability of the halogen could be due to its position to the carbonyl function in the keto tautomer (Scheme-44).

\[ \text{109} \xrightarrow{\text{ICl}} \text{110} \]

Scheme 44

The only work on electrophilic substitution of thieno[2,3-b]pyridine has been carried out by Klemm and his group.\textsuperscript{4} NMR studies of the reaction of thieno[2,3-b]pyridine with deuterio sulfonic acid at 98.5° showed that the proton at C\textsubscript{3} was replaced much more rapidly than that at C\textsubscript{2}. Bromination of the same compound with an excess of bromine in carbon tetrachloride-water led to a low yield (17\%) of the 2,3-dibromo derivatives, chlorination under the same conditions\textsuperscript{69-75} gave both mono and dichlorothieno[2,3-b]pyridine. Halogenation with elemental halogen in sulfuric acid - silver sulfate\textsuperscript{68} gave 3-halogenated compound (111) in moderate yields (Scheme-45).

\[ \text{1} \xrightarrow{X_2/H_2SO_4} \text{111 (a-c)} \]

(a)= X= Cl (26\%); (b)= X= Br (47\%); (c)= X= I (22\%)

Scheme 45
In the above case of bromination due to the presence of a buffer \(^{67}\) the yield of (111b) was increased (57%). Nitration of (111a-c) by mixed acid gave poor yields (22-47 %) of the 3-halogeno-2-nitrothieno[2,3-b]pyridine. Thieno[2,3-b]pyridine and ethylthieno[2,3-b]pyridine\(^{68}\) were nitrated at C\(_3\).

It is interesting to note that the pyridine ring in the thieno[2,3-b]pyridine-N-oxide (112) is more reactive towards electrophiles than is the thiophene ring\(^{69}\) (Scheme-46).

![Scheme 46](image)

A mechanism involving 1,3-dipolar addition to the nitrene moiety and subsequent electrophilic attack is proposed to account for the formation of the 5-nitro isomer (113).

Nucleophilic substitution

During nucleophilic substitution, a hydride ion is replaced by a strong nucleophilic species. In case of treatment of thienopyridines with organolithium compounds, metatalation of the thiophene ring (\(\alpha\) to the sulphur atom) is an obvious competition.

Thieno[2,3-b]pyridine when treated with n-butyl lithium at 25-35 °C, followed by mild oxidation, gave the 6-butyl derivative (115) and an appreciable quantity of starting material.\(^{48}\) At a lower temperature methyl lithium yielded a product consisting of 6-methylthieno[2,3-b]pyridine (9) and thieno[2,3-b]pyridine (1). In both instances the recovered starting material could well have arisen from hydrolysis (during work-up) of 2-lithio
treated with deuterium oxide, than water. In this case the recovered thieno[2,3-b]pyridine consisted approximately equal amounts of the 2-D (117) and 2-H (1) isomers (Scheme-47).

Scheme 47

Formylation of the lithio derivative (116) prepared at -70°, gave a good yield (66% ) of thieno[2,3-b]pyridine-2-aldehyde (118) (Scheme-48).

Scheme 48

Nucleophilic displacement of halogen atom from 3-bromothieno[2,3-b]pyridine (119) and 5-bromothieno[2,3-b]pyridine (121) gave 3-cyanothieno[2,3-b]pyridine
Nucleophilic displacement of halogen atom from 3-bromothieno[2,3-b]pyridine (119) and 5-bromothieno[2,3-b]pyridine (121) gave 3-cyanothieno[2,3-b]pyridine (120) and 5-cyanothieno[2,3-b]pyridine (122) respectively, by reacting them with copper(I) cyanide in refluxing dimethylformamide (Scheme-49).

Scheme 49

In the nucleophilic displacement of halogen atom in 4-chlorothieno[2,3-b]pyridine (124), it is clear that reaction does not occur readily. It is likely that electron release from the thiophene ring reduces the activating influence of the N-oxide group (Scheme-50).

Scheme 50
Reaction of active methylene group

In 4,6-dimethylthieno[2,3-b]pyridine (126) both the methyl groups on reaction with benzaldehyde gave a dibenzylidene derivative (127)(Scheme-51).

![Scheme 51]

Oxidation

In thienopyridine the possibility exists of oxidation at nitrogen (to the N-oxide) or at sulphur (to the sulfoxide or sulfone). Per-acids selectively oxidize the nitrogen atom in thieno[2,3-b]pyridine, but the preparation of sulfoxides and sulfones was less easily achieved as thieno[2,3-b]pyridine on oxidation with iodobenzene dichloride or chlorine water gave a low yield of addition product 2,3-dichloro-2,3-dihydrothieno[2,3-b]pyridine-S-oxide (128)(Scheme-52).

![Scheme 52]

The method was devised for the preparation of the sulfones of thieno[2,3-b]pyridine (129) by reaction with sodium hypochlorite and dilute hydrochloric acid.
Thieno[2,3-b]pyridine sulfone (129) acted as a dienophile toward anthracene, naphthacene and furan. Self condensation via Diels-Alder reaction also occurred to afford 8-(3-pyridyl)quinoline (130) on heating (Scheme-53). It would be expected that various oxidation of thienopyridine would result in destruction of the thiophene ring rather than the pyridine ring.74

![Scheme 53](image)

Reduction

Thienopyridine is resistant to reduction by tin-hydrochloric acid, since the parent system can be obtained by reductive dehalogenation of chloro derivatives. Quaternary salts are reduced to the N-alkyl-4,5,6,7-tetrahydrothieno[2,3-b]pyridine by sodium borohydride.75-79 The azo-methine bond in dihydro derivative is reduced by lithium aluminium hydride.80
Amino compound

The obvious route to 3-aminothienopyridine is reduction of the 3-nitro compound which has not been free of complications. It was found that treatment of 3-nitro thieno[2,3-b]pyridine (131) with tin-hydrochloric acid, gave the desired 3-amino derivative (132). But iron-hydrochloric acid gave only the diamine (134)\(^{61}\) (Scheme-54).

\[
\begin{align*}
\text{131} & \xrightarrow{\text{Fe/HCl}} \text{134} \\
\text{132} & \xrightarrow{\text{Sn/HCl}} \xrightarrow{\text{NHCOCH}_3} \text{133}
\end{align*}
\]

Scheme 54

An efficient method for the direct production of an acetylamino derivatives (133) from a nitro compound, involving reaction of the later with iron-acetic acid-acetic anhydride has been described.\(^{69}\) Both 4- and 5-nitrothieno[2,3-b]pyridine-N-oxide gave the amines on treatment with iron-acetic acid and tin-hydrochloric acid respectively, the N-oxide group also being removed during the reduction.\(^{70}\) 5-Aminothieno[2,3-b]pyridine (136) prepared from 5-acetylthieno[2,3-b]pyridine (20)\(^{70}\) readily gave Schiff's bases, whereas under the same or more vigorous conditions, 4-aminothieno[2,3-b]pyridine (135) failed to react with these aldehydes.\(^{70}\) Thus, 5-amino group was bound to be more reactive than 4-amino group.
5-Aminothieno[2,3-b]pyridine (136) closely resembled the analogous 3-aminoquinoline (137) behaving as a typical aromatic primary amine. It could be diazotized and the diazonium salt yielded the 5-bromo, 5-chloro, 5-hydroxy and 5-cyanothieno[2,3-b]pyridine under the usual conditions.

1.3 Reactions of o-aminosubstituted thieno[2,3-b]pyridine (1)\textsuperscript{82}

Substituted thieno[2,3-b]pyridines (I) are found to be very good intermediates for the preparation of tri / tetra cyclic heterocyclic ring system.

\[
R = R_1 = R_2 = \text{OH, NH}_2, \text{CN, COCH}_3, \text{COOC}_2\text{H}_5, \text{C}_6\text{H}_5, \text{sub. Phenyl}
\]
\[
R_3 = R_4 = \text{NH}_2 ; R_3 = R_4 = \text{COOH, COOC}_2\text{H}_5, \text{COPh, CN, CONH}_2, \text{CHO, CSNH}_2
\]
1.3.1 Synthesis of o-amino carbethoxy, o-amino carboxylic acid and o-amino ketones of thienopyridines


8-Substituted 7,9-dimethylpyrido[3', 2': 4, 5]thieno[3,2-d]pyrimidin-4-(3H)-ones (141) have been prepared by the same reaction starting from 5-substituted 2-carbethoxy-3-amino-4,6-dimethylthieno[2,3-b]pyridines (140) (Scheme-56).

\[
\text{NH}_2 \quad \text{HCONH}_2 \quad \text{NH}
\]

\[
138 \quad 139
\]

Scheme 55

\[
R = \text{H, NO}_2
\]

\[
\text{CH}_3 \quad \text{NH}_2 \quad \text{HCONH}_2 \quad \text{NH}_2 \quad \text{CH}_3
\]

\[
140 \quad 141
\]

Scheme 56

Similarly, pyridothienopyrimidine (143) and 2-methylpyridothienopyrimidine (144) were synthesized from novel 2-carbethoxy-3-aminothieno[2,3-b]pyridine (142) (Scheme-57).

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Gewald et al. synthesized pyrido[3', 2': 4, 5]thieno[3,2-d]pyrimidines with a substituent at position-4. Thus, 7,8,9-trisubstituted pyrido[3', 2': 4, 5]thieno[3,2-d]pyrimidin-4-(3H)-ones (146) were synthesized by the reaction of 4,5,6-trisubstituted 3-amino thieno[2,3-b]pyridines (145) with formamide (Scheme-58).

5,6,7,8-Tetrahydro-7-benzoylpyrido[4', 3': 4, 5]thieno[2,3-d]pyrimidin-4-(3H)-ones (148) was synthesized by formylation followed by amminative cyclization of 2-
Noravyan et al. synthesized 5,6,7,8-tetrahydro-7-isopropylpyrido[4', 3': 4, 5]thieno[2,3-d]pyrimidin-4-(3H)-ones (150) and 2-aryl-7-isopropyl-5,6,7,8-tetrahydro-pyrido[4', 3': 4, 5]thieno[2,3-d]pyrimidin-4-(3H)-ones (151) by reaction of 2-amino-3-carbethoxy-6-isopropyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine (149) with formamide and benzoyl chlorides followed by ammination respectively (Scheme-60).
4,6-Disubstituted 2-carbethoxy-3-aminothieno[2,3-b]pyridines (152) were saponified to give 4,6-disubstituted 3-aminothieno[2,3-b]pyridine-2-carboxylic acid (153) which was then cyclized with acetic anhydride to afford pyridothienooxazines (154) which were reacted with various amines to get 7,9-disubstituted 2-methylpyrido[3', 2': 4, 5]thieno[3,2-d]pyrimidin-4-(3H)-ones (155) (Scheme-61).

Dave et al. have reported the synthesis of 2-thioxo pyridothienopyrimidine (157) from 4,6-disubstituted 2-carbethoxy-3-aminothieno[2,3-b]pyridines (156) with various isothiocyanates in boiling pyridine which were s-methylated (158) using dimethylsulphate in basic medium (Scheme-62).
2,7,9-Trisubstituted 4-oxopyrido[3', 2': 4, 5]thieno[3,2-d]oxazines (160) were prepared by reacting 3-amino-2-carbethoxythieno[2,3-b]pyridines (159) with acetic anhydride, propionic anhydride, benzoyl chloride and H$_3$C$_2$COOCOCl give appropriate oxazine derivatives (Scheme-63).
Vieweg showed that acylated thieno[2,3-b]pyridines (161) were reacted with \(\omega\)-hydroxy alkylamino to give tricyclic 3-(\(\omega\)-hydroxy alkyl)pyrido[3', 2': 4, 5]thieno[3,2-d]pyrimidine-4(3H)-ones (162) which were further reacted with \(\alpha, \omega\)-diamino alkanes to give tetracyclic ring system (163) (Scheme-64).

\[
\begin{align*}
\text{161} & & \text{162} \\
 & & \\
R_1, R_2, & R_4, R_5 & R_1, R_2, & R_6, R_7 \\
R, & \text{COOR}_3 & \text{N} & - (\text{CH}_2)_n \text{R}_7 \\
\text{163} & & \\
R= \text{CH}_3, \text{C}_6\text{H}_5; & R_1= \text{H}, \text{CH}_3, \text{CH}_2\text{C}_6\text{H}_5; & R_2= \text{H}, \text{CH}_3, \text{4-BrC}_6\text{H}_4 \\
R_3= \text{CH}_3, \text{C}_2\text{H}_5; & R_4= \text{Ac}, \text{Bz}; & R_5= \text{H}; & R_6= \text{CH}_3, \text{C}_6\text{H}_5; & R_7= \text{OH}; & n=1-3
\end{align*}
\]

Scheme 64

Thieno[2,3-b]pyridine (164) when reacted with acetic anhydride, 2-carbethoxy-3-amino-4-phenyl-5-cyano-6-oxopyrido[3', 2': 4, 5]thieno[3,2-d]oxazine (165) were obtained which on reaction with appropriate primary amines transformed to 2-carbethoxy-3-amino-4-phenyl-5-cyano-6-oxopyrido[3', 2': 4, 5]thieno[3,2-d]pyrimidine (166) (Scheme-65).
o-Aminocarboxylates of thiено[2,3-b]pyridines (167) and thiено[2,3-c]pyridines (169) when reacted in acidic medium with cyanates, thiocyanates, cyanamides, acylcyanides and (un)substituted acetonitriles yielded 2,7,9-trisubstituted pyrido[3′, 2′: 4, 5]thieno[3,2-d]pyrimidine-4(3H)-ones (168) and 2,3,7-trisubstituted 5,6,7,8-tetrahydropyrido[4′, 3′: 4, 5]thieno[3,2-d]pyrimidine-4(3H)-ones (170) respectively (Scheme-66).
E. Kh. Ahmed have reported the synthesis of pyridothienopyrimidine. Thus 2-amino-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3,6-dicarboxylate (171) was reacted with ethoxy carbamoyl methylisothiocyanate in absolute alcohol to give diethyl-2-({[2-ethoxy-2-oxoethylamino]carbothionyl}amino)-4,5,6,7-tetrahydrothieno[2,3-b]pyridine-3,6-dicarboxylate (172) which was reacted with sodium ethoxide to afford ethyl-3-(2-ethoxy-2-oxoethyl)-4-oxo-2-thioxo-1,2,3,4,5,6,7,8-octahydropyrido[4',3':4,5]thieno[2,3-d]pyrimidine-7-carboxylate (173) which was further methylated with methyl iodide / NaOH to give (174) (Scheme-67).
2,3-Disubstituted 7-methyl-5,6,7,8-tetrahydropyrido[4', 3': 4, 5]thieno[2,3-d]pyrimidin-4(3H)-ones (177) have been prepared by condensing 2-amino-3-carbethoxy-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridines (175) with substituted imidates (176) (Scheme-68).

Several 4-substituted pyrido[3'', 2'': 4', 5']thieno[2', 3': 5, 6]pyrido[2,3-d]pyrimidines (180) were prepared from the 2-substituted 3-aminothieno[2,3-b]pyridines (178) with the reaction of malononitrile and Cl$_2$N'\(\text{Me}_2\)Cl' in presence of nucleophilic agents and 2-substituted 4-chloropyrido[3', 2': 4, 5]thieno[3,2-d]pyrimidines (179) were prepared by reacting (178) with various aldehyde and tosylalcohol and then with phosphorous pentachloride (Scheme-69).
2-Aminothieno[2,3-c]pyridine\textsuperscript{100} (181) was reacted with CS\textsubscript{2} in pyridine to produce pyridothienopyrimidine (182) (Scheme-\textsuperscript{70}).

Similarly the pyridothienopyrimidines (184)\textsuperscript{101} were synthesized via the reaction of pyridothiophene (183) with CS\textsubscript{2} and where further transformed to related fused heterocyclic system (Scheme-\textsuperscript{71}).
Khaltab et al\textsuperscript{102} showed that 4,5,6-trisubstituted 2-carbethoxy-3-aminothieno[2,3-b]pyridine (185) was reacted with hydrazine to give pyridine carbohydrazide intermediate. Which was further cyclized with triethyl orthoformate to give pyridothiopyrimidine (186) (Scheme-72).

4-Hydroxy-2-oxo-pyridothienopyridine (188)\textsuperscript{103} was prepared by reacted 2-acetyl-3-aminothienopyridine (187) with triethyl orthoformate (Scheme-73).
1.3.2 Reactions of o-aminocarboxamido or o-aminothiocarboxamido thienopyridine

In this approach 5,6,7-trisubstituted 2-amino-3-carboxamido-4,5,6,7-tetrahydrothieno[3,2-c]pyridines (189)\textsuperscript{104} were reacted with triethyl orthoformate or acetic anhydride to afford 2,6,7,8-tetrasubstituted 4-hydroxy-5,6,7,8-tetrahydropyrido[4', 3': 4, 5]thieno[2,3-d]pyrimidines (190) (Scheme-74).

\[
\begin{array}{c}
\text{(189)} \\
\text{CONH}_2 \\
\text{R}_1 \text{N} \text{R}_2 \\
\text{(190)} \\
\text{OH} \\
\text{N} \text{R} \\
\end{array}
\]

\[ R = \text{H, CH}_3; \text{R}_1 = \text{R}_3 = \text{H, C}_6\text{H}_5, 4\text{-ClC}_6\text{H}_4; \text{R}_2 = \text{CH}_3, \text{CH}_2\text{C}_6\text{H}_4, \]

iso-propyl, iso-butyl

Scheme 74

3-Amino-2-carboxamidothienopyridines (191)\textsuperscript{105} and 3-amino-2-thiocarboxamidothienopyridines (192) have been condensed with acetic anhydride to afford 7,9-disubstituted 2-methylpyrido[3', 2': 4, 5]thieno[3,2-d]pyrimidine-4(3H)-ones (193) and corresponding 4(3H)-thiones (194) respectively,\textsuperscript{70} similarly reaction of (191) and (190) with triethyl orthoformate gave 7,9-disubstituted pyrido[3', 2': 4, 5]thieno[3,2-d]pyrimidin-4(3H)-ones (195) and corresponding 4(3H)-thiones (196) respectively (Scheme-75).
2,7,9-Trisubstituted pyrido[3', 2': 4, 5]thieno[3,2-d]pyrimidine-4(3H)-ones (198) have been synthesized by the reaction of 4,6-disubstituted 2-carboxamido-3-aminothieno[2,3-b]pyridines (197) with acetic anhydride or triethyl orthoformate (Scheme 76).

Pyrido[4', 3': 4, 5]thieno[3,2-d]pyrimidine-4(3H)-one (200) have been obtained by the reaction between thieno[2,3-c]pyridine (199) with triethyl orthoformate (Scheme 77).
Yakovlev\textsuperscript{109} showed that 2,4,5,6-tetrasubstituted 3-aminothieno[2,3-b]pyridine (201) was reacted with triethyl orthoformate to give pyridothienopyrimidine (202) (Scheme-78).

\begin{align*}
\text{R} &= \text{N} \text{HC}_6\text{H}_5; \text{R}_1 = \text{H, N(CH}_3)_2; \text{R}_2 = \text{H, COOC}_2\text{H}_5; \text{R}_3 = \text{H, CH}_3
\end{align*}

Kadushkin\textsuperscript{110} used triethyl orthoformate as a one carbon component in the synthesis of pyridothienopyrimidinone (204) by using thieno[2,3-b]pyridines (203) (Scheme-79).
2-Substituted 3-amino-5-phenylazo-4,6-dimethylthieno[2,3-b]pyridine (205) was refluxed with triethyl orthoformate or acetic anhydride to give 5-phenylazopyrido thienopyrimidine (206) (Scheme 80).

1.3.3 Reaction of o-aminocarbonitriles of thienopyridine derivatives

7-Methyl-5,6,7,8-tetrahydropyrido[4', 3': 4, 5]thieno[2,3-d]pyrimidine-2,4(1H, 3H)-dithione (208) has been formed by the reaction of 7-methyl-2-amino-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carbonitrile (207) with K-xanthogenate (Scheme 81).
6,7,8-Trisubstituted 2,4-diamino-5,6,8-tetrahydropyrido[4', 3': 4, 5]thieno[2,3-d]pyrimidines (210) have been synthesized by the reaction of 5,6,7-trisubstituted 2-amino-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carbonitrile (209) with Chloroformidine hydrochloride (Scheme-82).

4,5,6-Trisubstituted 3-aminothieno[2,3-b]pyridine-2-carbonitrile (211) have been cyclized with formamide to yield 7,8,9-trisubstituted 4-aminopyrido[3', 2': 4, 5]thieno[3,2-d]pyrimidines (212) (Scheme-83).
6-Substituted 2-amino-4,5,6,7-tetrahydrothieno[2,3-b]pyridine-3-carbonitriles (213) were condensed with triethyl orthoformate to give corresponding N-ethoxymethylene derivatives (214), which on subsequent cyclization with hydrazine hydrate gave 7-substituted 3-amino-5,6,7,8-tetrahydropyrido[4', 3': 4, 5]thieno[2,3-d]pyrimidine-4-imines (215) (Scheme 84).

Thiocarboxamides (217) were obtained, when \( \text{H}_2\text{S} \) gas was bubbled in 4,6-disubstituted 3-aminothieno[2,3-b]pyridine-2-carbonitrile (216), in basic medium, which on cyclization with triethyl orthoformate afforded 7,9-disubstituted pyrido[3', 2': 4, 5]thieno[3,2-d]pyrimidine-4(3H)-thiones (218) (Scheme 85).
4-Amino-7-isopropyl-5,6,7,8-tetrahydropyrido[4', 3': 4, 5]thieno[2,3-d]pyrimidines \((220)\) have been synthesized by the reaction between 3-amino-6-isopropyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carbonitriles \((219)\) and formamide (Scheme-86).

Sharanin et al\(^{120}\) have synthesized 4-amino-7,8-cyclohexyl-9-(2-furyl)pyrido[3', 2': 4, 5]thieno[3,2-d]pyrimidine \((222)\) by reacting corresponding thienopyridine \((221)\) with formamide (Scheme-87).
7,8,9-Trisubstituted 2-((ω-chloroalkyl)-pyrido[3', 2': 4, 5]thieno[3,2-d]pyrimidin-4-ones (224) were prepared by reacting 3-aminothieno[2,3-b]pyridine-2-(ω-hydroxyalkyl)carboxamide (223) with Vilsmeier reagent (dimethylformamide and phosphorous oxychloride) (Scheme-88).

2-Amino-3-carbethoxy-4,5,6,7-tetrahydro-6-benzylthieno[2,3-c]pyridine (225) was reacted with various nitriles in presence of hydrochloric acid gas to afford 2-substituted-5,6,7,8-tetrahydro-7-benzylpyrido[4', 3': 4, 5]thieno[2,3-d]pyrimidin-4-ones (226) (Scheme-89).

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3-Amino-4,6-dimethylthieno[2,3-b]pyridine-2-carboxamide (227) was reacted with carbon disulfide to give 7,9-dimethyl-1,2,3,4-tetrahydro-2-thioxopyrido[3',2':4,5]thieno[3,2-d]pyrimidin-4-ones (228) (Scheme-90).

3-Amino-4,6-dimethylthieno[2,3-b]pyridine-2-carboxamide (229) was cyclocondensed with urea, formic acid and acetic anhydride to afford 3-amino-7,9-dimethyl-1H-pyrido[3',2':4,5]thieno[3,2-d]pyrimidin-2,4-diones (230) (Scheme-91).
Scheme 91