Synthesis, Reactions and Characterization of 6-thioxo-1,6-dihydro-2,3′-bipyridine-5-carbonitrile

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Abstract

3-acetylpyridine 1 reacted with ethyl formate to afford the corresponding sodium salt of 3-hydroxy-1-(pyridin-3-yl)prop-2-en-1-one 2 in acceptable yield. The reaction of such sodium salt with 2-cyanoethanethioamide 3 in basic medium yield 6-thioxo-1,6-dihydro-2,3′-bipyridine-5-carbonitrile 4 which reacted with several active-halogen containing reagents 5a-j to afford the corresponding 2-alkylthio derivatives in few cases (6i,j) and thieno[2,3-b]pyridines 7a-g as the products of Thorpe-Ziegler cyclization. The structures of the newly synthesized compounds were assigned by spectroscopic data and elemental analysis.

Keywords: Synthesis, Reactions, Characterization, 6-thioxo-1,6-dihydro-2,3′-bipyridine-5-carbonitrile.

1. Introduction

During the past few decades many results have been published in the area of the synthesis, characterization and biological evaluation of heterocyclic compounds containing a pyridine ring connected to or fused with different heterocyclic systems. Thieno[2,3-b]pyridine and Pyridothienopyrimidine derivatives form a very interesting class of compounds because of their sufficient biological and pharmaceutical activities and their chemistry is consequently now receiving considerable attention Furuya et al., 1996; Cho et al., 1998; Miki et al., 1999; N. Suzuki et al., 1997; Furuya et al., 2000; Furuya et al., 1998; Sohda et al., 1996 and Leistner et al., 1986. We have previously reported synthesis, reactions, characterization and biological evaluation of several derivatives of this ring system (Abdel-Fattah et al., 2013; Attaby et al.,
As a continuation of these studies we undertook the synthesis and reactions of the title compounds, which might have shown good biological and medicinal applications.

2. Results and Discussion

Our approach to the synthesis of the target compounds started from the reaction of 3-acetylpyridine 1 with ethylformate in dry ether containing sodium methoxide under stirring at room temperature to afford the corresponding sodium salt of 3-hydroxy-1-(pyridin-3-yl)prop-2-en-1-one 2. Compound 2 reacted with 2-cyanoethanethioamide 3 in aqueous piperidine acetate under reflux for 30 minutes to give brown crystalline product 4. The $^1$H NMR spectra of the resulting product displayed two signals readily recognizable as arising from pyridine protons ($\delta$ 7.16-8.93, as multiplet signals) and NH ($\delta$ 14.36, as singlet broad signal). Its IR spectrum revealed the presence of the bands corresponding to the NH (3181 cm$^{-1}$), CN (2215 cm$^{-1}$) and C=S (1582 cm$^{-1}$) groups. Moreover, its mass spectrum gave the parent peak at m/z = 213 which corresponding also, to the base peak that represent the molecular weight of the assigned structure 4 (cf. Scheme 1). Treatment of compound 4 with chloroacetone 5a in sodium methoxide-methanol mixture under stirring at room temperature for 25 minutes yielded product 7a. The IR of 7a revealed the absence of the bands corresponding to the CN group and instead showed the bands corresponding to NH (3363, 3262 cm$^{-1}$) and intramolecular H-bonding C=O (1616.06 cm$^{-1}$), Kislyi V. P.(1996). Furthermore, its mass spectrum gave very intensive peak at m/z = 269 which represents parent, base peak and the molecular weight of the molecular formula C$_{14}$H$_{11}$N$_3$OS of the assigned structure (cf. Exp. Part, Scheme 1). In addition to the previously mentioned peak other peaks represented by the following fragmentation pattern and gave further elucidation of the assigned structure (cf. Fragmentation Pattern of compound 7a).
Compound 4 was also, reacted with 3-chloropentan-2,4-dione (5b) under the same above-mentioned experimental condition to afford unexpectedly compound 7a via the non-isolable intermediate 6b. The formation of 7a rationalized by assuming that the reaction proceeded through the dehydrochlorination to give the non-isolable intermediate I that underwent Thorpe-Ziegler cyclization to give the imino derivative II which hydrolyzed to give the final obtained 7a (cf. Eq. 1). It is important to report here that compound 7a obtained by the two pathways was identical in all physical and chemical properties (cf. Experimental Part).

Similarly, compound 4 reacted with each of chloroacetamide (5c), chloroacetonitrile (5d), ethyl chloroacetate (5e), under the same above-mentioned experimental conditions to afford the corresponding thieno[2,3-b]pyridines 7c-e. The IR spectra of these reaction products showed the absorption bands corresponding to the newly formed NH$_2$ group, while the absorption bands of CN function disappeared. The $^1$H NMR spectral data revealed the signals of pyridine protons as well as that of CONH$_2$ in case of 7c and COOCH$_2$CH$_3$ in case of 7e respectively. Also, elemental analysis data were the basis that be considered to account with the structures 7c-e represented by scheme 1. Moreover, the mass spectra of compounds 7c-e gave an intensive molecular ion peaks at m/z = 269, 270 and 252 which corresponding the molecular weights of the assigned structures (cf. Scheme 1 and Exp. Part). An authentic sample of the compound 7e obtained through the reaction of 4 with ethyl 3-chloro-2-oxobutanoate (5f) under the same experimental condition. The formation of 7e via this pathway rationalized by assuming that the reaction proceeded through the dehydrochlorination to give the non-isolable intermediate I that underwent Thorpe-Ziegler cyclization to give the imino derivative II which hydrolyzed to give the final obtained 7e (cf. Eq. 2). It is important to report here that compound 7e obtained by the two pathways was identical in all physical and chemical properties (m.p., IR, $^1$H NMR and mass spectral data, cf. Exp. Part). In a similar way, compound 4 reacted with 2-bromo-1-(phenyl, 4-chlorophenyl, 4-methylphenyl)ethanone 5g-i to afford the corresponding thieno[2,3-b]pyridine derivatives 7g-i whose structures were established by considering the data of elemental analysis, IR, $^1$H NMR (cf. Exp. Part). Moreover, their mass spectral were convinced with the assigned structures (cf. Fragmentation pattern) where:

**Compound 7g** gave the peak (M$^+$) at m/z = 331, 70.29% which corresponding to the molecular weight of the assigned structure; base peak at m/z = 330, M$^+$-H, 100%; peak at m/z = 77, 83.23%; peak at m/z = 105, 40%.

**Compound 7h** gave the peak (M$^+$) at m/z = 365, 72.42% which corresponding to the molecular weight of the assigned structure; base peak at m/z = 364, M$^+$-H, 100%; peak at m/z = 111, 50.69%; peak at m/z = 139, 29.14%, in addition to the isotope peaks of all fragments containing Cl at m/z = 113, 17.48%; 141, 10.25%.

**Compound 7i** gave the peak (M$^+$) at m/z = 345, 66.00% which corresponding to the molecular weight of the assigned structure; base peak at m/z = 344, M$^+$-H, 100%; peak at m/z = 91, 72.64%; peak at m/z = 119, 39.31%.

In contrast to the behavior of compound 4 towards the reaction with each of the reagents 5a-i, it has been found that compound 4 reacted with chloroacetic acid (5j) under the same above-mentioned experimental condition to afford the corresponding [(5-cyano-2,3'-bipyridin-6-yl)sulfanyl]acetic acid 6j. The IR of each of 6j showed the bands of CN groups and its $^1$H NMR spectra revealed the signals of -CH$_2$-, COOH protons. Moreover, its mass spectrum gave
the peak corresponding to M+ in addition to the peaks corresponding to the removal of -COOH, -CH₂COOH, -SCH₂COOH from the parent molecule (cf. Exp. Part). Further confirmation of each of 7c,d structure arose from their reactions with formic acid to afford one and the same product 8 whose structure was established by considering the data of elemental analysis, IR, ¹H NMR and mass spectral data (cf. Exp. Part).

![Diagram of chemical reactions and structures](image)

### Scheme 1

<table>
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<th>Comp.</th>
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Obtaining compound 8 from the reaction of 7d rationalized by assuming the partial hydrolysis of CN at 2-position of 7d to give CONH₂ group which cyclized with formic acid to give 8 (cf. Scheme 2).

This study was extended to shed more light on the synthetic potentiality of ethoxycarbonyl group in ethyl 3-amino-6-(pyridin-3-yl)thieno[2,3-b]pyridine-2-carboxylate (7e). Thus, compound 7e reacted with hydrazine hydrate under reflux for 6 hours to afford the corresponding 3-amino-6-(pyridin-3-yl)thieno[2,3-b]-pyridine-2-carbohydrazide 9. The IR spectrum of this reaction product showed the absorption bands at 3438, 3289, 3196 corresponding to NH, NH₂ groups and its mass spectrum gave the parent peak (M⁺) at m/z = 285, 40.73% as well as other peaks corresponding to the fragment M⁺-NHNH₂ (254, 100 %) and M⁺-CONH₂NH, 226, 20.74 %) and this gave further elucidation of 9 structure (cf. Exp. Part). 2-Carbohydrazide derivative 9 is an active intermediate and excellent starting material for the synthesis of several heterocyclic systems. Thus, compound 9 reacted with each of benzaldehyde 11a or benzylidenepropanedinitrile (10a) and 4-
methoxybenzaldehyde (11b) or (4-methoxybenzylidene)propanedinitrile (10b) afforded the corresponding 3-amino-N'-arylmethylidene)-6-(pyridin-3-yl)thieno[2,3-b]pyridine-2-carbohydrazides 12a,b respectively. The IR and mass spectral data as well as the data of elemental analyses used as the good evidences for the structures 12a,b (cf. Exp. Part). Furthermore, compound 9 reacted with reagents 13, 15, 17 and 19 afforded the corresponding 7-(pyridin-3-yl)pyrido[3',2':4,5]thieno[3,2-d]pyrimidin-4(3H)-ones 14, 16, 18 and 20 respectively whose structures were elucidated by considering the data of elemental analyses and IR spectra. Moreover, their mass spectra gave the corresponding M⁺ at m/z = 323 (17.13%); 351 (32.95); 309 (25%) and 393 (38.77%) respectively (cf. Exp. Part and Scheme 3). The formation of the unexpected product 18 explained through the reaction of DMF-DMA with compound 9 to afford the non-isolable products I and II and the latter was methylated with the excess DMF-DMA to give 18 (cf. Eq. 3).

On the other hand, the formation of compound 20 proceeded through step wise reaction started with the acetylation of NH₂ on the thiophene ring followed by both ring closure and diacetylation of NH₂ on the pyrimidine ring (cf. Eq. 3). Also, compound 9 reacted with each of phenylisothiocyanate (21) and carbon disulfide (23) in pyridine under reflux afforded 2-[(phenylamino)-1,3,4-oxadiazol-2-yl]-6-(pyridin-3-yl)thieno[2,3-b]pyridin-3-amine (22) and 5-[3-amino-6-(pyridin-3-yl)thieno[2,3-b]-pyridin-2-yl]-1,3,4-oxadiazole-2-thiol (24) respectively whose structures elucidated by considering the data of IR, mass and elemental analyses (cf. Scheme 4 and Exp. Part).

**Fragmentation Pattern of compounds 7g, 7h, 7i**

![Fragmentation Pattern of compounds 7g, 7h, 7i](image)

- **Base peak, M⁺-H⁺ (100%) at m/z = 330 (7g); 364 (7h); 344 (7i)**
- **M⁺, at m/z = 331, 70.27% (7g, Z = H); 365, 72.42%, (7h, Z = Cl); 345, 66.00% (7i, Z = CH₃)**
- **m/z = 105 (40.07%, 7g); 139 (29.14%), 141 (10.25%, 7h); 119 (39.31%, 7i)**
- **m/z = 77 (83.32%, 7g); 111 (50.69%), 113 (17.48%, 7h); 91 (72.64%, 7i)**
3. Experimental

Melting points were measured with a Gallenkamp apparatus and are uncorrected. IR spectra from KBr discs were recorded on a Bruker Vector 22 FT-IR spectrophotometer. $^1$H and $^{13}$C NMR spectra were determined in DMSO-d$_6$ and CDCl$_3$ at 300 MHz on a Varian Mercury VX spectrometer using TMS as an internal standard. Chemical shifts are expressed as $\delta$ or ppm. Mass spectra were recorded on a GCMS-QP 1000 EX spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt.

**Synthesis of compound 4 (General procedures):** An equimolar amount of 3-hydroxy-1-(pyridin-3-yl)prop-2-en-1-one 2 (0.17 g, 1.0 mmol), cyanoethanethioamide (3) (0.1 g, 1.0 mmol) and piperidine acetate (0.5 mL) was heated under reflux for 30 mins. The solid obtained was collected by filtration and crystallized from ethanol to give compound 4: Brown crystals, m.p. 238°C; IR (v cm$^{-1}$): 3428(NH), 2215(CN) and 1582 (C= S); MS (m/z): 213 (M$^+$, 100% corresponding to the molecular formula C$_{11}$H$_7$N$_3$S of the assigned structure), 212 (M$^+$- H, 20.5 %), 180(M$^+$- SH, 11.2 %) and 154(M$^+$- HNCS, 3.4%). $^1$H NMR (δppm): 7.15–8.93 (m, 6H, pyridinylH’s) and 14.36 (br, 1H, NH). Anal. for C$_{11}$H$_7$N$_3$S (213), Calcd./Found (%): C (61.95/61.60) H (3.31/3.40) N (19.70/19.42) S (15.04/14.90).

**Synthesis of compounds of 6j and 7a-j:** A solution of 4 (0.5 mmol, 0.106g) and the appropriate reagent 5a-j (0.5 mmol) in methanol containing sodium methoxide (prepared by 0.6 g of sodium in 40 mL methanol) was stirred at room T for 3 h. The product that formed was collected by filtration, washed with cold ethanol, and then recrystallized from ethanol to give 7a-j and 6j respectively.
[(5-Cyano-2,3'-bipyridin-6-yl)sulfanyl]acetic acid: Pale yellow crystals, m.p. 165°C; IR (ν cm⁻¹): 2750-3255(OH), 2219(CN) and 1709 (CO); MS (m/z): 271 (M⁺, 100% corresponding to the molecular formula C₁₃H₉N₃O₂S of the assigned structure), 254 (M⁺- OH, 67.52 %), 226(M⁺- COOH, 18.63 %), 212(M⁺- CH₂COOH, 12.8%), 180(M⁺- SCH₂COOH, 2.25 %). Anal. for C₁₃H₉N₃O₂S (271), Calcd./Found (%): C (57.55/57.59) H (3.34/3.35) N 15.49/15.50) S (11.82/11.80).

1-[3-Amino-6-(pyridin-3-yl)thieno[2,3-b]pyridin-2-yl]ethanone 7a: Yellow crystals, m.p. 272 °C; IR (ν cm⁻¹): 3363, 3262( NH₂), 3077 (pyridinyl CH) 2924 (aliphatic CH) and 1616 (CO with H- bonding); MS (m/z): 269 ( M⁺, 100% corresponding to the molecular formula C₁₄H₁₁N₃OS of the assigned structure), 254 (M⁺- CH₃, 81.54 %), 226(M⁺- COCH₃, 25.13 %) and 191(M⁺- pyridinyl ring, 0.29 %). Anal. for C₁₄H₁₁N₃OS (269), Calcd./Found (%): C (62.43/62.20) H (4.12/3.90) N 15.60/15.30) S (11.91/11.60).
3-Amino-6-(pyridin-3-yl)thieno[2,3-b]pyridin-2-carboxamide 7c: Pale yellow crystals, m.p. 296°C; IR (ν cm⁻¹): 3425, 3328, 3270, 3126 (2 NH₂), and 1678 (amidic CO); MS (m/z): 270 (M⁺, 100% corresponding to the molecular formula C₁₃H₁₀N₄OS of the assigned structure), 269 (M⁺ - H, 1.24 %), 254 (M⁺ - NH₂, 11.45 %) 253 (M⁺ - NH₂, H 57.71 %), 226 (M⁺ - CONH₂, 9.83 %) and 225 (M⁺ - CONH₂, H 27.94 %). Anal. for C₁₃H₁₀N₄OS (270), Calcd./Found (%): C (57.76/57.40) H (3.73/3.90) N (20.73/20.30) S (11.86/11.60).
Scheme 3
Scheme 4

Ethyl-3-amino-6-(pyridin-3-yl)thieno[2,3-b]pyridin-2-carboxylate 7e: Yellow crystals, m.p. 284 °C; IR (ν cm⁻¹): 3422, 3269 (NH₂), and 1672 (H bonding ester CO); MS (m/z): 299 (M⁺, 2.46% corresponding to the molecular formula C₁₅H₁₃N₃O₂S of the assigned structure), 254 (M⁺-OEt, 17.40 %), 253 (M⁺-OEt, H, 65.74 %) 226(M⁺-COOEt, 9.56 %) and 225(M⁺-COOEt, H 26.52 %). Anal. for C₁₅H₁₃N₃O₂S (299), Calcd./Found (%): C (60.18/60.00) H (4.38/4.10) N (14.04/13.80) S (10.71 /10.50).

3-Amino-6-(pyridin-3-yl)thieno[2,3-b]pyridin-2-carbonitrile 7d: Yellow crystals, m.p. 284 °C; IR (ν cm⁻¹): 3388, 3339 (NH₂), and 2189 (CN); MS (m/z): 252 (M⁺, 100 % corresponding to the molecular formula C₁₃H₈N₄S of the assigned structure), 236 (M⁺-NH₂, 1.27 %) and 226(M⁺-CN, 8.77 %). Anal. for C₁₃H₈N₄S (299), Calcd./Found (%): C (61.89/61.70) H (3.20/3.10) N (22.21/22.00) S (12.71 /12.60).

[3-Amino-6-(pyridin-3-yl)thieno[2,3-b]pyridin-2-yl](phenyl)methanone 7g: Yellow crystals, m.p. 228°C; IR (ν cm⁻¹): 3351, 3256( NH₂), and 1595(C=C aromatic); MS (m/z): 331 (M⁺, 70.27% corresponding to the molecular formula C₁₉H₁₃N₃O₅S of the assigned structure), 330 (M⁺-H, 100 %), 226(M⁺-COPh, 10.71 %), 254(M⁺-Ph, 5.5 %), 105(COPh, 40 %) and 77(Ph, 83.22 %). Anal. for C₁₉H₁₃N₃OS (331), Calcd./Found (%): C (68.86/68.50) H (3.20/3.10) N (12.68/12.40) S (9.68/9.50).

[3-amino-6-(pyridin-3-yl)thieno[2,3-b]pyridin-2-yl](4-chlorophenyl)methanone 7h: Yellow crystals, m.p. 262 °C; IR (ν cm⁻¹): 3359, 3260( NH₂), 3073(aromatic CH) and
1595(C=C aromatic); MS (m/z): 367 ( $M^+$ + 2, 27.84%) 365 ( $M^+$, 72.42% corresponding to the molecular formula C$_9$H$_{12}$ClN$_3$OS of the assigned structure), 364 (M$^{2+}$ - H, 100 %), 226(M$^+$- COPhCl, 12.07 %), 139(COPhCl, 29.14 %), and 111(PhCl, 50.69 %). Anal. for C$_9$H$_{12}$ClN$_3$OS (365), Calcd./Found (%): C (62.88/62.40) H (3.68/3.30) N (11.49/11.10) S (8.76/8.50).

[3-Amino-6-(pyridin-3-yl)thieno[2,3-b]pyridin-2-yl]4-methylphenyl)methane 7i: Yellow crystals, m.p. 262 °C; IR (ν cm$^{-1}$): 3356, 3258( NH$_2$), 3066(aromatic CH) and 1595, 1470(C=C aromatic); MS (m/z): 345 ( M$^+$, 66 % corresponding to the molecular formula C$_{20}$H$_{15}$N$_3$OS of the assigned structure), 344 (M$^{2+}$ - H, 100 %), 226(M$^+$- COPh-CH$_3$, 8.99 %), 119(COPh-CH$_3$, 39.31 %); and 91(PhCH$_3$, 72.64 %). $^1$H NMR (δ ppm): 2.39(s, 3H, CH$_3$) and 7.33–9.35 (m, 12H, Ar, pyridinyl and NH H’s). Anal. for C$_{20}$H$_{15}$N$_3$OS(345), Calcd./Found (%): C (69.54/69.40) H (4.38/4.00) N (12.17/11.80) S (9.28/8.80).

3-Amino-6-(pyridin-3-yl)thieno[2,3-b]pyridine-2-carboxylic acid 7j: Yellow crystals, m.p. 298 °C; IR (ν cm$^{-1}$): 3358, 3278(NH$_2$), 3056(aromatic CH) and 1654(H-bonded CO); MS (m/z): 271 ( M$^+$, 100% corresponding to the molecular formula C$_{13}$H$_{10}$N$_3$OS of the assigned structure), 270 ( M$^{2+}$ - H, 67.10%), 254 (M$^{2+}$- OH, 23%), 226(M$^+$- COOH, 45.31 %); $^1$H NMR (δ ppm): 5.79(s, br., 2H, NH$_2$), 7.12–8.21 (m, 6H, pyridinyl H’s) and 12.3(s, br., 1H, COOH); Anal. for C$_{13}$H$_{10}$N$_3$OS (271), Calcd./Found (%): C (57.55/57.51) H (3.34/3.30) N (15.49/15.51) S (11.82/11.85).

Synthesis of 8 (General Procedure): A solution of each of 7c or 7d (0.270g, 0.299g; 1mmol) in formic acid (15mL) was heated under reflux for 5 h; the excess solvents were evaporated. The solids so formed after cooling were collected by filtration, dried, and crystallized from the dioxiane to give 8.

7-(Pyridin-3-yl)pyrido[3',2':4,5]thieno[3,2-d]pyrimidin-4(3H)-one 8: Brown crystals, m.p. > 300 °C; IR (ν cm$^{-1}$): 3178(NH, and 1674(amidic CO); MS (m/z): 280 ( M$^+$, 100% corresponding to the molecular formula C$_{14}$H$_{11}$N$_3$OS of the assigned structure), 279 ( M$^{2+}$ - H, 55.12%), 237 (M$^+$- HNCO, 12.11%); $^1$H NMR (δ ppm): 6.98–8.01 (m, 6H, pyridinyl H’s), 8.66(1H, s, Pyrimidine H’s) and 10.1(s, br., 1H, NH); Anal. for C$_{14}$H$_{11}$N$_3$OS (280), Calcd./Found (%): C (59.99/60.01) H (2.88/2.90) N (19.99/20.01) S (11.44/11.45).

Synthesis of 9 (General Procedure): A solution of 17c (0.299g; 1mmol) in hydrazine hydrate (15mL) and ethanol (20 mL) was heated under reflux for 5 h; the excess solvents were evaporated. The solids so formed after cooling were collected by filtration, dried, and crystallized from the dioxiane to give 9.

3-Amino-6-(pyridin-3-yl)thieno[2,3-b]pyridine-2-carboxyhydrazide 9: Yellow crystals (76%), m.p. = 298 °C; IR (ν cm$^{-1}$): 3438, 3289, 3196(NH, NH$_2$), 3049 (pyridinyl CH); MS: 285 (M$^+$, 33.19% corresponding to the molecular formula C$_{13}$H$_{11}$N$_3$OS of the assigned structure), 254(M$^{2+}$-HNH$_2$, 100%); 226(M$^+$-CONHNH$_2$, 21.99 %); $^1$HNMR (DMSO-D$_6$) (δ ppm): 2.11(s, br., 2H, NH$_2$ of hydrazidic group), 4.23(s, br., 2H, NH$_2$ at C-3 of thiophene ring), and 7.33–9.35 (m, 7H, pyridinyl and NH hydrazidic protons). Anal. for C$_{13}$H$_{11}$N$_3$OS (285) Calcd./Found (%): C (54.72/54.40) H(3.89/3.59) N(24.55/24.20) S(11.24/11.10).

Synthesis of 12a,b (General Procedure): A solution of 9 (0.28g, 1mmol) and (benzylidene or 4-methoxybenzylidene)-malononitrile 10a,b (0.15g, 0.18, 1mmol) or benzaldehyde or 4-methoxybenzaldehyde 11a,b (0.11, 0.14g, 1mmol) in pyridine (15 mL) and ethanol (20 mL) was heated under reflux for 2 h, the excess solvents were evaporated. The solids so formed after
cooling were collected by filtration, dried, and crystallized from the dioxane to give 12a,b respectively.

3-Amino-N’-[phenylmethylidene]-6-(pyridin-3-yl)thieno[2,3-b]pyridine-2-carbohydrazide (12a): Yellow crystals (86%), m.p. = 264°C; \( \text{IR} (\text{v cm}^{-1}) \): 3395, 3281 (NH), 3163 (NH), 3024 (aromatic-CH) and 1642 (CO); MS: 373 (M\(^+\), 373, 63.12%, which corresponded to the molecular weight of the assigned structure), 269 (M\(^+\) - PhCH=N, 12.76%), 254 (M\(^+\) - PhCH=N-NH, 7.45%), 226 (M\(^+\) - PhCH=N-NHCO, 23.23%); Anal, for C\(_{20}\)H\(_{15}\)N\(_3\)O\(_2\)S (373) Calcd./Found(%): C(65.34/64.40) H(4.02/4.10) N(18.77/18.42) S(8.57/8.60).

3-Amino-N’-[4-(methoxyphenyl)methylidene]-6-(pyridin-3-yl)thieno[2,3-b]pyridine-2-carbohydrazide (12b): orange crystals (75%), m.p. = 282°C; \( \text{IR} (\text{v cm}^{-1}) \): 3409, 3287 (NH), 3155 (NH); MS: 403 (M\(^+\), 45.27% corresponding to the molecular formula C\(_{21}\)H\(_{17}\)N\(_3\)O\(_3\)S of the assigned structure), 372 (M\(^+\) - OCH\(_3\), 6.5%); 254 (M\(^+\) - NHN=CH-C\(_6\)H\(_4\)-p-OMe, 100%); 226 (M\(^+\) - CONHN=CH-C\(_6\)H\(_4\)-p-OMe, 22.2%); \(^1\text{HNMR} \quad (\delta \text{ppm}): 2.11\text{(s, 3H, CH\(_3\)), 4.12}\text{(s, br., 2H, NH\(_2\) at C-3 of thiophene nucleus),} and 7.12-9.72 \text{(m, 12H, pyridinyl, phenyl and -NH-N=CH- protons); Anal, for C\(_{21}\)H\(_{17}\)N\(_3\)O\(_3\)S (403) Calcd./Found(%): C(62.53/62.40) H(4.22/4.10) N(7.57/7.50) S(9.91/9.80).}

**Synthesis of 14**: A solution of 9 (0.28g 1mmol) and formic acid 13 (15 ml) was heated under reflux for 6 h. The excess solvent was evaporated. The solid so formed after cooling was collected by filtration, dried, and crystallized from ethanol and dioxane to give 14.

N-[4-Oxo-(pyridin-3-yl)pyrido[3',2':4,5]thieno[3,2-d]pyrimidin-3(4H)/yl]formamide (14): Yellow crystals (87%), m.p. = 324°C; \( \text{IR} (\text{v cm}^{-1}) \): 3438 (NH), 3058 (aromatic-CH) and 1686 (CO); MS: 323 (M\(^+\), 17.13% which corresponded to the molecular weight), 322 (M\(^+\) - H, 17.47%), 294 (M\(^+\) - CHO, 14.65%), 279 (M\(^+\) - NHCHO, 16.40%); \(^1\text{HNMR} \quad (\delta \text{ppm}): 6.06\text{(s, 1H, NH) and 7.54–9.37}\text{(m, 7H, pyrimidinyl H’s and C\(_2\)H) and 11.47}\text{(s, 1H, CHO). Anal, for C\(_{15}\)H\(_{13}\)N\(_2\)O\(_2\)S (323) Calcd./Found(%): C(55.73/55.30) H(4.22/4.10) N(7.72/7.60) S(9.91/9.80).}

**Synthesis of 16**: A solution of 9 (0.28g, 1mmol) and triethylorthoformate (10 mL) 15 was heated under reflux for 4 h; the excess solvent was evaporated. The solid so formed after cooling was collected by filtration, dried, and crystallized from dioxane to give 16.

Ethyl[4-oxo-(pyridin-3-yl)pyrido[3',2':4,5]thieno[3,2-d]-pyrimidin-3(4H)-yl]limidioformate (16): Yellow crystals (77%), m.p. = 250°C; \( \text{IR} (\text{v cm}^{-1}) \): 3026 (aromatic-CH) and 1670 (CO); MS: 351 (M\(^+\), 32.95% which corresponded to the molecular weight), 280 (M\(^+\) - N=C=OEt, 100%) and 279 (M\(^+\) - N=CH-OEt, /20.81%); \(^1\text{HNMR} \quad (\delta \text{ppm}): 1.40\text{(t, 3H, }J = 7.2\text{ Hz -OCH\(_2\)CH\(_3\)), 4.42}\text{(q, 2H, }J = 7.2\text{ Hz, -OCH\(_2\)CH\(_3\)), 7.55–8.68}\text{(m, 9H, pyridinyl H’s and C\(_2\)H) and 9.37 (s, 1H, N=CH-OEt); Anal, for C\(_{17}\)H\(_{13}\)N\(_2\)O\(_2\)S (351) Calcd./Found (%): C(58.12/58.00) H(3.70/3.52) N(19.94/19.60) S(9.11/9.00).}

**Synthesis of 18**: A solution of 9 (0.28g, 1mmol) and dimethylformamide-dimethylacetel 17 (0.12g, 1mmol) in dry xylene (15 mL) was heated under reflux for 5 h. The excess solvent was evaporated and the solid so formed after cooling was collected by filtration, dried, and crystallized from ethanol/ dioxane to give 18.

3-Methylamino-7-pyridin-3-ylpyrido[3',2':4,5]thieno[3,2-d]pyrimidin-4(3H)-one (18): Yellow crystals (70%), m.p. = 264°C; \( \text{IR} (\text{v cm}^{-1}) \): 3040 (aromatic-CH) and 1704 (CO); MS: 309 (M\(^+\), 45.12%, corresponded to the molecular weight of the assigned structure), 294(M\(^+\) - CH\(_3\), 33.12%), 279(M\(^+\) - NHCH\(_3\), 65.82%); \(^1\text{HNMR} \quad (\delta \text{ppm}): 2.21\text{(s, br., 1H, CH\(_3\)-NH-), 2.34}\text{(s, 3H, CH\(_2\)-NH-), 7.65–9.33}\text{(m, 7H, pyrimidine and pyridine protons); Anal, for
C_{15}H_{11}N_{2}OS (309) Calcd./Found (%): C(58.24/58.25) H(3.58/3.62) N(22.64/22.62) S(17.59/17.60).

**Synthesis of 20:** A solution of 9 (0.28g, 1mmol) and acetic anhydride (15 ml) was heated under reflux for 6 h. The excess solvent was evaporated and the solid so formed was collected by filtration, dried, and crystallized from the dioxane to give 20.

**N-Acetyl-N-[2-methyl-4-oxo-7-(pyridin-3-yl)pyrido[3',2';4,5]thieno[3,2-d]-pyrimidin-3(4H)-yl]-acetamide (20):** Yellow crystals (78%), m.p. = 210°C; IR (v cm⁻¹): 1737, 1692 (Two CO); MS: 393 (M⁺, 38.77% which corresponding to the molecular weight), 350 (M⁺ - COCH₃, 2.18%), 309 (M⁺ -2COCH₃, 100%), 293 (M⁺ -N(COCH₃)₂, 5.13%); ¹H NMR (DMSO-D₆-D₆) (δppm): 1.12(s, 3H, CH₃), 2.67(s, 6H, two CH₃ at pyrimidine ring). 2.67(s, 6H, two CH₃CO protons), 7.32-9.35(m, 6H, pyridine protons); Anal, for C_{10}H_{15}N_{2}O_{3}S (393) Calcd./Found (%): C(58.01/58.12) H(3.84/3.64) N(17.80/17.50) S(8.15/8.10).

**Synthesis of 22 and 24 (General Procedure):** A solution of 9 (0.28g, 1mmol) and each of phenyl isothiocyanate (0.14g, 1mmol) and carbon disulphide (5 ml) and in pyridine (15 ml) was heated under reflux for 5h, cooled, poured onto ice-cold water, and neutralized with drops of acetic acid. The solids so formed were collected by filtration, dried, and crystallized from the ethanol-dioxane mixture to give 22 and 24 respectively.

2-[5-(Phenylamino)-1,3,4-oxadiazol-2-yl]-6-(pyridin-3-yl)thieno[2,3-b]pyridin-3-amine (22): Yellow crystals (78%), m.p. = 260°C; IR (v cm⁻¹): 3421, 3272 (NH₂), 3118(NH), 1674 (CO); MS: 386 (M⁺, 13.59 % which corresponding to the molecular weight), 282 (M⁺ - =CNHC₆H₅, 14.34%), 268 (M⁺ - N=CNHC₆H₅, 5.93%); Anal, for C_{20}H_{14}N_{2}OS (386) Calcd./Found (%): C(62.16/61.85) H(3.65/3.47) N(21.75/21.48) S(8.30/8.12).

5-[3-Amino-6-(pyridin-3-yl)thieno[2,3-b]pyridin-2-yl]-1,3,4-oxadiazole-2-thiol (24): Yellow crystals (67%), m.p. = 260-C; IR (vcm⁻¹): 3424, 3354 (NH₂); MS: 327 (M⁺, 36.74% which corresponding to the molecular weight), 326 (M⁺ -H, 28.63%), 310 (M⁺ -NH₂, H 29.11%), 293 (M⁺ -SH, H 30.15%), 226 (M⁺ - oxadiazole-2- thiol, 3.2%) and 101(oxadiazole-2- thiol, 12.53%); ¹H NMR (DMSO-D₆-D₆) (δppm): 3.12(s, 1H, SH at oxadiazolo ring), 4.73(s, br., 2H, NH₂ at thiophene ring), 7.88-9.35(m, 6H, pyrine protons); Anal, for C_{16}H_{10}N_{2}O_{2} (327) Calcd./Found (%): C(51.36/51.12) H(2.77/2.54) N(21.39/21.14) S(19.59/19.20).

**References**


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