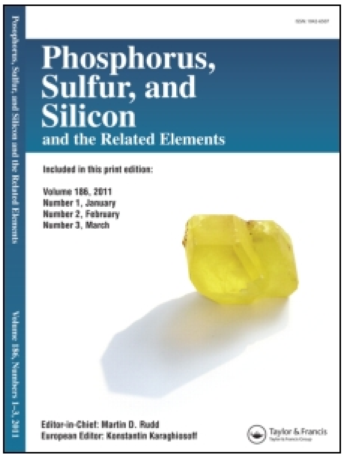

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Synthetic Utility of Enaminonitrile Moiety in Heterocyclic Synthesis: Synthesis of Some New Thienopyrimidines

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*The hitherto unknown 3-amino-5-bromo-4, 6-dimethylthieno [2, 3-b] pyridine-2-carbonitrile (**4**) was condensed with p-anisaldehyde affording the Schiff base (**5**). Acylation of the thienopyridine derivative (**4**) using freshly distilled acetic anhydride gave a mixture of mono and diacetyl derivatives (**6**) and (**7**). Condensation of (**4**) with triethylorthoformate yielded the ethoxymethyleneamino derivative (**8**), which was treated with hydrazine hydrate to give the hydrazide derivative (**9**), which in turn was converted to a triazolopyrimidine derivative (**10**) upon treatment with freshly distilled acetic anhydride. Thiation of (**4**) with carbon disulfide afforded the pyrimidine dithione derivative (**11**), which was alkylated with ethyl iodide to give the di-s-ethylpyrimidine derivative (**12**).On the other hand, treatment of (**4**) with formamide yielded the aminopyrimidine derivative (**13**), whereas its treatment by formic acid produced the thienopyrimidinone derivative (**14**). Chlorination of (**14**) with a mixture of phosphorus pentachloride and phosphorus oxychloride gave the chloropyrimidine derivative (**15**), which in turn afforded the hydrazide derivative (**9**) upon treatment with hydrazine hydrate. Hydrazinolysis of ethyl-3-amino-5-bromo-4,6-dimethylthieno[2,3-b]pyridine-2-carboxylate (**17**) gave the hydrazino derivative (**18**), which in turn was converted to 8-bromo-7,9-dimethyl-3-formylaminopyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**19**) and 8-bromo-3-diacetylamino-2,7,9-trimethylpyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**20**) upon treatment with formic acid and freshly distilled acetic anhydride, respectively.*

Keywords Antimicrobial activity; enaminonitrile; thienopyridine; thienopyrimidine

INTRODUCTION

In continuation of our present program in the utility of enaminonitrile and enaminoester moieties in the synthesis of different

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heterocyclic systems,[1–4] and due to the pronounced biological and pharmacological activities of thienopyrimidine derivatives,[5–7] such as anticancer,[8] antiviral,[9] antitumor,[10] anti-inflammatory,[11] antimicrobial,[12] antifungal,[13] antihistaminic,[14] analgesic,[15] antibiotic,[16,17] antidepressant,[18,19] antihypertensive,[19,20] antiulcer,[21] bactericidal,[22,23] blood platelet aggregation inhibitory,[24–26] fungicidal,[27–29] herbicidal,[30] hypersensitivity inhibitory,[31] insecticidal,[30,32] immunomodulatory, and oncostatic.[33] The therapeutic importance of thienopyrimidines prompted us to construct several analogs by exotic combinations of groups and active moieties. The present work aimed to synthesize some new derivatives of this class of compounds utilizing 3-amino-5-bromo-4, 6-dimethylthieno[2, 3-*b*]pyridine-2-carbonitrile.

RESULTS AND DISCUSSION

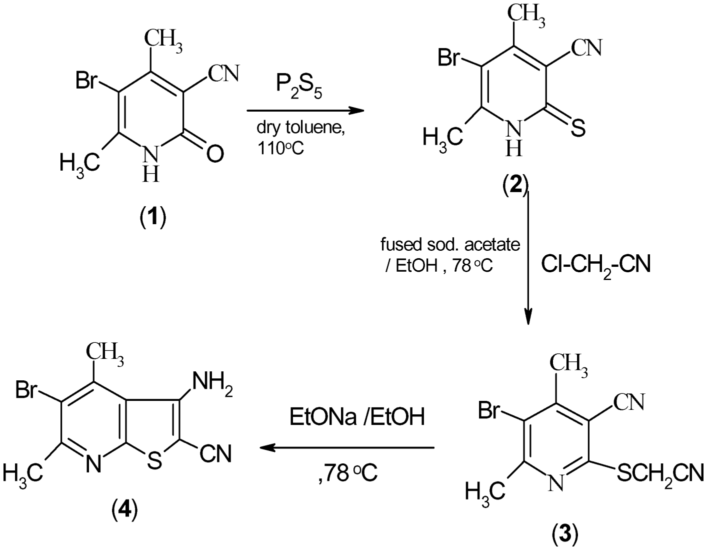
The key starting material, 3-amino-5-bromo-4,6-dimethylthieno[2,3-*b*]pyridine-2-carbonitrile (**4**), has been obtained in fair yield via the cyclization of 5-bromo-2-[(cyanomethyl)thio]-4,6-dimethylnicotinonitrile (**3**) with sodium ethoxide in ethanolic solution.[34] Pyridine derivative (**3**) was obtained by treatment the thione derivative (**2**) with chloroacetonitrile.[34] It was found that (**2**) was obtained upon thiation of (**1**)by phosphorous pentasulfide (Scheme 1). 3-Cyano-4,6-dimethyl-2-(1*H*)-pyridone was obtained according to Bardhan's method.[35] Bromination of the latter compound using N-bromo succinimide in carbon tetrachloride containing a few drops of hydrogen peroxide (30%) afforded 5-bromo-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**1**).

The structure of compound (**1**) was confirmed by its mp and mixed mp and by comparison of these with the literature value,[36] although it was prepared by an alternative method (Br_2/glacial AcOH).

The structure of (**4**) was established by elemental analysis as well as spectral data (IR,^{1}H-NMR, MS) and chemically via condensation with p-anisaldehyde to give the corresponding Schiff base (**5**) (Scheme 2) .

The effect of acetic anhydride on enaminonitrile has been investigated in many publications,[37,38] and it has been found that the nature of the product depends mainly upon the time of the reaction. In our present work, acylation of the starting material (**4**) with acetic anhydride afforded a mixture of both mono and diacetyl derivatives (**6**) and (**7**), respectively (Scheme 2).

Alternatively, treatment of the thienopyridine derivative (**4**) with triethyl orthoformate[39] afforded 5-bromo-2-cyano-4, 6-dimethyl-3-ethoxy-methyleneaminothieno[2,3-*b*]pyridine (**8**), which upon

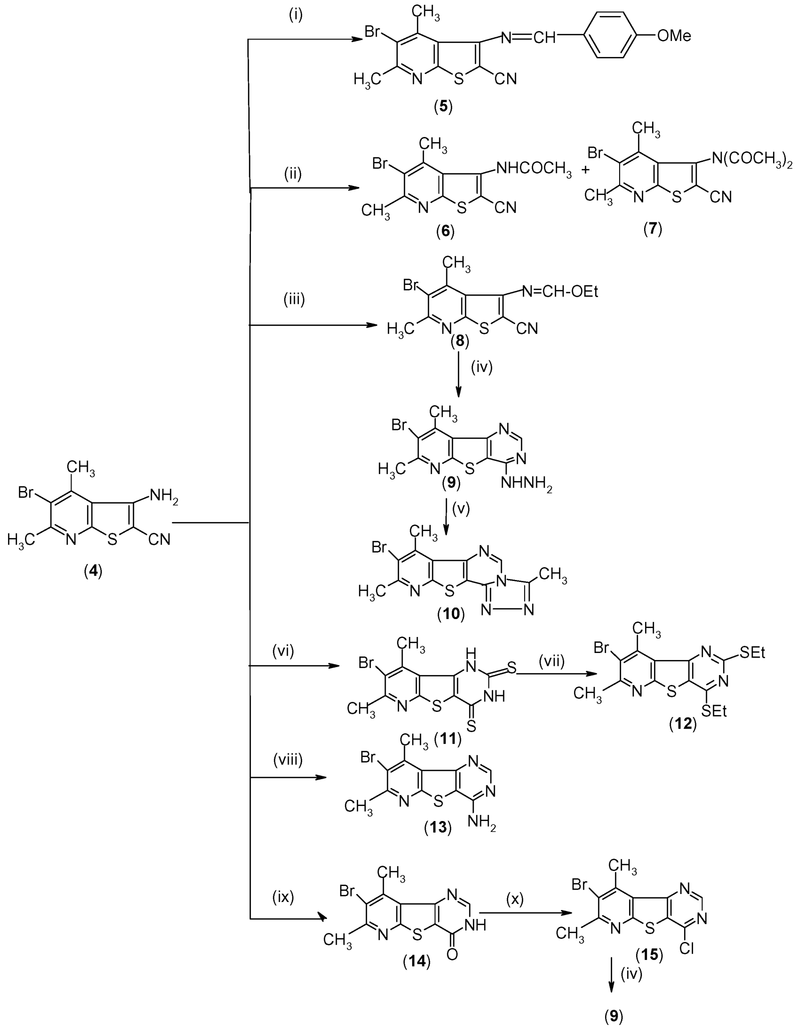


SCHEME 1

hydrazinolysis[40,41] gave 8-bromo-4-hydrazino-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (**9**), whose structure was confirmed by elemental analysis as well as spectral data. Furthermore, chemical proof is achieved via acetylation with acetic anhydride to yield the triazolopyrimidine derivative (**10**) in fair yield (Scheme 2).

Thiation of the thienopyridine derivative (**4**) using carbon disulfide yielded 8-bromo-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-2,4-(1*H*,3*H*)-dithione (**11**), which was alkylated by ethyl iodide in dry acetone to afford 8-bromo-2,4-di(ethylthio)-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (**12**) (Scheme 2).

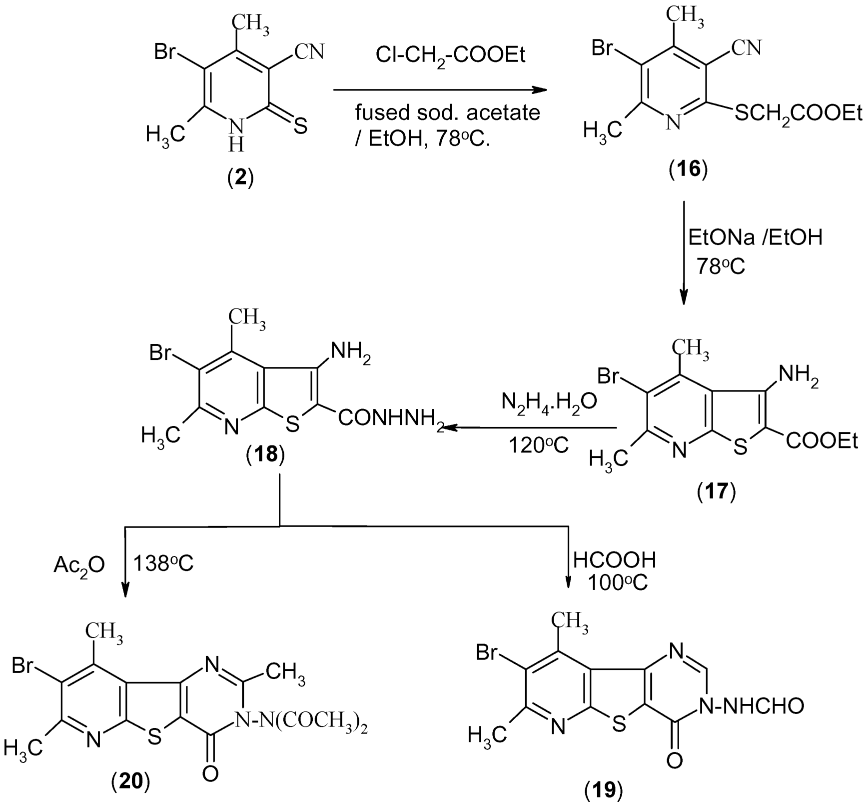
Treatment of the thienopyridine derivative (**4**) with formamide[7,42] gave the expected aminopyrimidine derivative (**13**) in quantitative yield (Scheme 2). Furthermore, the reaction of (**4**) with formic acid[7,43] gave 8-bromo-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4-(3*H*)-one (**14**), which underwent chlorination[44] using a mixture of phosphorus pentachloride and phosphorus oxychloride as a chlorinating reagent to give the chloropyrimidine derivative (**15**). The structure of (**15**) was elucidated via elemental analysis and also spectral data, and chemically through the reaction with hydrazine hydrate to afford 8-bromo-4-hydrazino-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (**9**) (Scheme 2).



(i) P-anisaldehyde /EtOH, Piperidine, 78°C(ii) Ac_2O,138°C; (iii)$CH(OEt)_3$,146°C;(iv) $N_2H_4.H_2O$,EtOH,78°C;(v)Ac_2O,138°C; (vi) CS_2 /dry pyridine ,114 °C;(vii)EtI /EtOH,78°C ;(viii)$HCONH_2$, 210 °C ; (ix) HCOOH,100°C;(x) PCl_5 / $POCl_3$, 105 °C

SCHEME 2

On the other hand, alkylation of the thione derivative (**2**) using ethyl chloroacetate[34] afforded pyridine derivative (**16**), which in turn was cyclized[34] to give ethyl-3-amino-5-bromo-4,6-dimethylthieno[2,3-*b*]pyridine-2-carboxylate (**17**) whose structure was confirmed by elemental analysis as well as spectral data (Scheme 3).



SCHEME 3

Furthermore, reaction of (**17**) with hydrazine hydrate[45–47] yielded 3-amino-5-bromo-4,6-dimethylthieno[2,3-*b*]pyridine-2-carbohydrazide (**18**), which in turn was subjected to react with formic acid and freshly distilled acetic anhydride to give 8-bromo7,9-dimethyl-3-formylaminopyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (**19**) and 8-bromo-3-diacetylamino-2,7,9-trimethylpyrido[3′,2′:4,5]thieno[3,2-*d*] pyrimidin-4-(3*H*)-one (**20**), respectively (Scheme 3).

EXPERIMENTAL (Tables I and II)

All melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. The infrared spectra were recorded using potassium bromide disks on a Pye Unicam SP-3-300 infrared spectrophotometer. ^{1}H-NMR experiments were run at 300 MHz on a Varian

TABLE I Characterization Data of Prepared Compounds

			Analysis (Required/Found)			
Compound No.	MP °C (color)	Yield % (solvent)	Mol. Formula (M. wt)	C	H	N
(2)	279–280	71	$C_8H_7BrN_2S$	39.52	2.90	11.52
	(yellow)	T	(243.12)	39.20	2.62	11.21
(3)	146–148	89	$C_{10}H_8BrN_3S$	42.57	2.86	14.89
	(yellow)	P_a	(282.16)	42.43	2.61	14.58
(4)	258–260	80	$C_{10}H_8BrN_3S$	42.57	2.86	14.89
	(yellow)	E	(282.16)	42.36	2.54	14.60
(5)	190–192	56	$C_{18}H_{14}BrN_3OS$	54.01	3.53	10.50
	(yellow)	P_a	(400.29)	53.89	3.30	10.28
(6)	274–276	50	$C_{12}H_{10}BrN_3OS$	44.46	3.11	12.96
	(white)	B	(324.20)	44.19	2.92	12.65
(7)	130–132	45	$C_{14}H_{12}BrN_3O_2S$	45.91	3.30	11.47
	(yellow)	P_b	(366.23)	45.59	2.99	11.25
(8)	118–120	51	$C_{13}H_{12}BrN_3OS$	46.16	3.58	12.42
	(yellow)	P_a	(338.22)	45.89	3.27	12.13
(9)	260–262	84	$C_{11}H_{10}BrN_5S$	40.75	3.11	21.60
	(white)	A	(324.20)	40.47	2.87	21.25
(10)	238–240	45	$C_{13}H_{10}BrN_5S$	44.84	2.89	20.11
	(white)	P_a	(348.22)	44.57	2.62	19.99
(11)	302–305	50	$C_{11}H_8BrN_3S_3$	36.87	2.25	11.73
	(orange)	P_y	(358.30)	36.55	1.97	11.45
(12)	120–122	60	$C_{15}H_{16}BrN_3S_3$	43.47	3.89	10.14
	(white)	P_a	(414.41)	43.15	3.57	9.89
(13)	> 360	46	$C_{11}H_9BrN_4S$	42.73	2.93	18.12
	(white)	D	(309.18)	42.46	2.65	17.87
(14)	> 360	64	$C_{11}H_8BrN_3OS$	42.60	2.60	13.55
	(white)	A	(310.17)	42.28	2.27	13.28
(15)	176–178	54	$C_{11}H_7BrClN_3S$	40.20	2.15	12.79
	(white)	P_b	(328.62)	39.96	1.98	12.50
(16)	78–80	58	$C_{12}H_{13}BrN_2O_2S$	43.78	3.98	8.51
	(yellow)	P_a	(329.21)	43.50	3.70	8.22
(17)	202–204	66	$C_{12}H_{13}BrN_2O_2S$	43.78	3.98	8.51
	(yellow)	P_b	(329.21)	43.50	3.72	8.26
(18)	240–242	63	$C_{10}H_{11}BrN_4OS$	38.11	3.52	17.78
	(yellow)	D	(315.18)	37.89	3.25	17.53
(19)	258–260	63	$C_{12}H_9BrN_4O_2S$	40.81	2.57	15.86
	(pale yellow)	E	(353.19)	40.49	2.30	15.62
(20)	218–220	55	$C_{16}H_{15}BrN_4O_3S$	45.40	3.57	13.24
	(white)	E	(423.28)	45.16	3.28	12.98

A: Acetic acid,B: Benzene, D: Dioxane, E: Ethanol, P_a: Petroleum ether (60–80°C), P_b: Petroleum ether (80–100°C), P_y: Pyridine

TABLE II ^{1}**H-NMR, MS, and IR Data of Prepared Compounds**

Compound No.	^{1}H-NMR (δ in ppm)	MS (m/z %)	IR CM^{-1}		
			$\nu_{NH,OH}$	$\nu_{C\equiv N}$	$\nu_{C=O}$
(2)	3.50 (s, 1H), 2.57 (s, 3H), 2.44 (s, 3H)	$[M+2]^{\cdot+}$(244, 57.1%), $[M]^{\cdot+}$(242, 52.4%), 197 (43.6%), 118 (49.0%), 81 (41.4%)	3174	2221	—
(3)	4.05 (s, 2H), 2.77 (s, 3H), 2.58 (s, 3H)	$[M+2]^{\cdot+}$(283, 69.0%), $[M]^{\cdot+}$(281, 85.4%), 256 (100.0%), 255 (30.8%), 131 (74.9%), 81 (19.2%)	—	2222	—
(4)	6.51 (s, NH_2), 2.84 (s, 3H), 2.51 (s, 3H)	$[M+2]^{\cdot+}$(283, 74.8%), $[M]^{\cdot+}$(281, 62.2%), 202 (23.1%), 134 (6.3%), 131 (15.9%), 70 (100.0%)	3333, 3238	2203	—
(5)	8.62 (s,1H), 7.95—7.92 (d, 2H), 7.06—7.03 (d, 2H), 3.92 (s, 3H), 2.91 (s, 3H), 2.79 (s, 3H)	$[M+2]^{\cdot+}$(401, 75.1%), $[M]^{\cdot+}$(399, 100.0%), 398 (77.3%), 370 (25.9%), 292(33.5%)	—	2204	—
(**6**)	7.38 (s, 1H), 2.82 (s, 3H), 2.65 (s, 3H), 2.32 (s, 3H)	—	3223	2217	1679
(7)	2.84 (s, 3H), 2.59 (s, 3H), 2.43 (s, 6H)	$[M+2]^{\cdot+}$(367, 00.0%), $[M]^{\cdot+}$(365, 00.0%), 323 (38.2%), 283 (56.6%), 281 (100.0%), 244 (10.4%)	—	2222	1723
(8)	8.03 (s, 1H), 4.49—4.47 (q, 2H), 2.84 (s, 3H), 2.81 (s, 3H), 1.47 (t, 3H)	$[M+2]^{\cdot+}$(339, 84.7%), $[M]^{\cdot+}$(337, 75.5%), 292 (79.9%), 281 (95.8%), 215 (13.6%)	—	2206	—
(9)	8.20 (s, 1H), 7.32 (s, 1H), 5.82 (s, 2H), 3.00 (S, 3H), 2.72 (s, 3H)	$[M+2]^{\cdot+}$(325, 100.0%), $[M]^{\cdot+}$(323, 65.8%), 308 (26.8%), 281 (29.2%), 186 (15.8%)	3305, 3115	—	—
(10)	9.33 (s, 1H), 3.15 (s, 3H), 2.88 (s, 3H), 2.72 (s, 3H)	$[M+2]^{\cdot+}$(349, 81.3%), $[M]^{\cdot+}$(347, 100.0%), 350 (14.3%), 268 (35.5%)	—	—	—
(11)	4.33 (s, 1H), 2.83 (s, 3H), 2.62 (s, 3H), 2.02 (s, 1H)	$[M+2]^{\cdot+}$(359, 00.0%), $[M]^{\cdot+}$(357, 00.0%), 325 (31.1%), 291 (33.6%), 210 (31.1%)	3412	—	—

(Continued on next page)

TABLE II ^{1}H-NMR, MS, and IR Data of Prepared Compounds *(Continued)*

Compound No.	^{1}H-NMR (δ in ppm)	MS (m/z %)	IR CM^{-1}		
			$\nu_{NH,OH}$	$\nu_{C\equiv N}$	$\nu_{C=O}$
(12)	3.46—3.44 (q, 2H), 3.38—3.27 (q, 2H), 3.20 (s, 3H), 2.86 (s, 3H), 1.47 (t, 6H)	$[M+2]^{\cdot+}$(416, 22.0%), $[M]^{\cdot+}$(414, 31.3%), 382 (56.9%), 324 (25.9%)	—	—	—
(13)	8.54 (s, 1H), 7.58 (s, 2H), 3.09 (s, 3H), 2.74 (s, 3H)	$[M+2]^{\cdot+}$(310, 96.3%), $[M]^{\cdot+}$(308, 70.1%), 293 (27.1%), 229 (30.8%), 200 (74.8%)	3457, 3292	—	—
(14)	11.89 (s, 1H), 7.87 (s, 1H), 2.81 (s, 3H), 2.64 (s, 3H)	$[M+2]^{\cdot+}$(311, 100.0%), $[M]^{\cdot+}$(309, 80.1%), 281 (38.3%), 202 (30.1%)	3446	—	1659
(**15**)	9.11 (s, 1H), 3.23 (s, 3H), 2.90 (s, 3H)	$[M+2]^{\cdot+}$(329, 100.0%), $[M]^{\cdot+}$(327, 66.2%), 248 (45.1%), 184(11.3%)	—	—	—
(**16**)	4.25—4.22 (q, 2H), 3.96 (s, 2H), 2.65 (s, 3H), 2.59 (s, 3H), 1.28 (t, 3H)	$[M+2]^{\cdot+}$(330, 11.4%), $[M]^{\cdot+}$(328, 12.1%), 256 (49.2%), 255 (100.0%), 209 (13.8%)	—	2218	1735
(**17**)	6.17 (br, 2H), 4.39—4.32 (q, 2H), 2.92 (s, 3H), 2.79 (s, 3H), 1.42 (t, 3H)	$[M+2]^{\cdot+}$(330, 76.7%), $[M]^{\cdot+}$(328, 38.9%), 285 (23.0 %), 282 (100.0%), 234 (22.0%)	3452, 3338	—	1668
(**18**)	8.99 (br, 1H), 6.75 (br, 2H), 4.42 (br, 2H), 2.71 (s, 3H), 2.65 (s, 3H)	$[M+2]^{\cdot+}$(316, 24.6%), $[M]^{\cdot+}$(314, 21.9%), 285 (100.0%), 283 (94.0%), 255 (25.3%)	3491, 3304, 3255, 3202	—	1651
(**19**)	8.46 (s, 1H), 8.14 (s, 1H), 5.04 (s, 1H), 3.14 (s, 3H), 2.87 (s, 3H)	$[M+2]^{\cdot+}$(354, 53.7%), $[M]^{\cdot+}$(352, 51.7%), 297 (100.0%), 295 (89.6%), 269 (24.8%)	3210	—	1679
(**20**)	3.14 (s, 3H), 2.86 (s, 3H), 2.52 (s, 3H), 2.52 (s, 6H)	$[M+2]^{\cdot+}$(424, 20.2%), $[M]^{\cdot+}$(422, 30.5%), 380 (46.2%), 365 (35.9%), 340 (100.0%)	—	—	1752, 1696

Mercury VX-300 NMR spectrometer using TMS as internal standard in deuterated chloroform or deuterated dimethylsulphoxide. Chemical shifts are quoted δ. The mass spectra were recorded on a Shimadzu GCMS-QP-1000EX mass spectrometers at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University. All the newly synthesized compounds gave satisfactory elemental analyses.

5-Bromo-4,6-dimethyl-2-thioxo-1, 2-dihydropyridine-3-carbonitrile (2)

A mixture of (**1**) (10 mmol, 2.26 g) and phosphorus pentasulfide (5 mmol, 1.11 g) in dry toluene (25 mL) was heated at reflux for 4 h. The solid product that was separated out while hot was collected, dried, and recrystallized to give (**2**).

5-Bromo-2-[(cyanomethyl)thio]-4,6-dimethylnicotinonitrile (3)

A mixture of (**2**) (10 mmol, 2.42 g) and chloroacetonitrile (11 mmol, 0.75 mL) in ethanol (20 mL) in the presence of fused sodium acetate (15 mmol, 1.23 g) was heated at reflux for 1.5 h and left to cool. The solid product that formed was filtered and washed with water, dried, and recrystallized to afford (**3**).

3-Amino-5-bromo-4,6-dimethylthieno[2, 3-*b*] pyridine-2-carbonitrile (4)

To a hot solution of (**3**) in ethanol (20 mL), a few drops of sodium ethoxide solution (prepared by dissolving 0.5 g sodium metal in 20 mL ethanol) was added dropwise. The solution was heated at reflux for 15 min and allowed to cool. The solid that formed was collected, dried, and recrystallized to give (**4**).

5-Bromo-3-{[(4-methoxyphenyl)methylene]amino}-4, 6-dimethylthieno[2,3-*b*]pyridine-2-carbonitrile (5)

To a hot solution of (**4**) (1.7 mmol, 0.5 g) in ethanol (20 mL) containing a few drops of piperidine, p-anisaldehyde (1.7 mmol, 0.24 mL) was added, and the reaction mixture was heated under reflux for 2 h. The precipitated solid that separated on cooling was collected by filtration, dried, and recrystallized to furnish (**5**).

N-(5-Bromo-2-cyano-4,6-dimethylthieno[2,3-*b*]pyridin-3-yl)acetamide (6) and *N*-Acetyl-*N*-(5-bromo-2-cyano-4,6-dimethylthieno[2,3-*b*]pyridin-3-yl)acetamide (7)

A mixture of (**4**) (1.7 mmol, 0.5 g) and freshly distilled acetic anhydride (10 mL) was heated at reflux for 3 h. The solid that deposited after distilling the excess solvent was collected and recrystallized to afford (**6**) and (**7**).

N.B.: The diacetylamino derivative (**7**) was authentically prepared by acetylating the monoacetylamino derivative (**6**) using freshly distilled acetic anhydride.

5-Bromo-2-cyano-4,6-dimethyl-3-ethoxymethyleneaminothieno[2,3-*b*]pyridine(8)

A mixture of (**4**) (1.7 mmol, 0.5 g) and triethyl orthoformate (10 mL) was heated at reflux for 2 h. An excess of triethyl orthoformate was removed by distillation under reduced pressure. The solid obtained was filtered, dried, and recrystallized to afford (**8**).

8-Bromo-4-hydrazino-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (9)

Method A

To a hot solution of (**8**) (1.48 mmol, 0.5 g) in ethanol (20 mL), hydrazine hydrate (0.5 mL) was added, and the reaction mixture was heated at reflux for 2 h. The solid product that was separated out while hot was collected, dried, and recrystallized to afford (**9**).

Method B

To a hot solution of (**15**) (1.5 mmol, 0.5 g) in ethanol (20 mL), hydrazine hydrate (0.5 mL) was added dropwise while the solution was heated at reflux for 2 h. The solid product that separated out while hot was collected, washed with ethanol, dried, and recrystallized to afford (**9**).

4-Bromo-3,5,9-trimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]1,3,4-triazolo[1,2-*f*]pyrimidine (10)

A mixture of (**9**) (0.92 mmol, 0.3 g) and freshly distilled acetic anhydride (10 mL) was heated at reflux for 5 h. The solid that deposited after distilling off the excess solvent was collected and recrystallized to afford (**10**).

8-Bromo-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dithione (11)

A mixture of (**4**) (1.7mmol, 0.5 g) and carbon disulfide (10 mL) in dry pyridine (20 mL) was heated at reflux for 6 h. Upon cooling, the precipitated solid was collected, dried, and recrystallized to afford (**11**).

8-Bromo-2,4-di(ethylthio)-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (12)

A hot solution of (**11**) (1.54 mmol, 0.55 g) in dry acetone (20 mL) and ethyl iodide (1.54 mmol, 0.47 mL) was heated at reflux for 10 h. The solid product that separated out while hot was collected, dried, and recrystallized to afford (**12**).

4-Amino-8-bromo-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine(13)

A mixture of (**4**) (1.7 mmol, 0.5 g) and formamide (10 mL) was heated at reflux for 4 h. The precipitated solid while hot was filtered, washed with water, dried, and recrystallized to give (**13**).

8-Bromo-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (14)

A mixture of (**4**) (1.7 mmol, 0.5 g) and formic acid (10 mL) was heated at reflux for 1.5 h. The solid product that was separated out while hot was collected, washed with water, dried, and recrystallized to afford (**14**).

8-Bromo-4-chloro-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (15)

A mixture of (**14**) (0.16 mmol, 0.5 g) and phosphorus pentachloride (0.16 mmol, 0.5 g) in phosphorus oxychloride (10 mL) was heated in a water bath at 100°C for 10 h. The reaction mixture was poured into water, and the precipitated solid was filtered, washed with water, dried, and recrystallized to afford (**15**).

Ethyl[(5-bromo-3-cyano-4,6-dimethylpyridin-2-yl)thio] acetate (16)

A mixture of (**2**) (10 mmol, 2.42 g) and ethyl chloroacetate (11 mmol, 0.75 mL) in ethanol (20 mL) in the presence of fused sodium acetate (15 mmol, 1.23 g) was heated at reflux for 1.5 h and left to cool. The solid product that deposited was filtered, washed with water, dried, and recrystallized to afford (**16**).

Ethyl 3-amino-5-bromo-4,6-dimethylthieno[2,3-*b*] pyridine-2-carboxylate (17)

To a hot solution of (**16**) in ethanol (20 mL), a few drops of sodium ethoxide solution (prepared by dissolving 0.5 g sodium metal in 20 mL ethanol) was added .The solution was heated at reflux for 15 min and allowed to cool. The solid product that formed was collected, dried, and recrystallized to give (**17**).

3-Amino-5-bromo-4,6-dimethylthieno[2,3-*b*] pyridine-2-carbohydrazide (18)

Method A

A mixture of (**17**) (15 mmol, 4.92 g) and hydrazine hydrate (15 mL) was heated at reflux for 2 h. The separated solid was filtered, triturated with ethanol, dried, and recrystallized to afford (**18**).

Method B

A mixture of (**16**) (15 mmol, 4.92 g) and hydrazine hydrate (15 mL) was heated at reflux in a water bath at 100°C for 2 h. The precipitated solid product was washed several times with ethanol and recrystallized to afford (**18**).

8-Bromo-7,9-dimethyl-3-formylaminopyrido[3′,2′:4,5] thieno[3,2-*d*]pyrimidin-4(3*H*)-one (19)

A mixture of (**18**) (1.59 mmol, 0.5 g) and formic acid (20 mL) was heated at reflux for 4 h. The cooled reaction mixture was diluted with water, and the precipitated solid was recrystallized to afford (**19**).

8-Bromo-3-diacetylamino2,7,9-trimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H)*-one (20)

A mixture of (**18**) (1.59 mmol, 0.5 g) and freshly distilled acetic anhydride (20 mL) was heated at reflux for 3 h. The solid that precipitated upon cooling was recrystallized to afford (**20**).

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