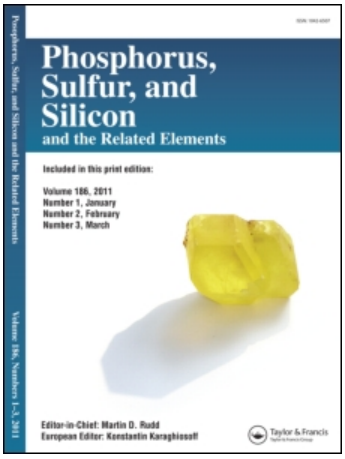

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Cyanothioacetamide in Heterocyclic Synthesis: A Novel Synthesis of Styrylpyridinethione, Styrylthieno[2,3-b]pyridine, Styrylpyrazolo[3,4-b]pyridine, Pyrido[2',3':3,4]pyrazolo[5,1-a]pyrimidine, Pyrido[3',2':4,5]thieno[3,2-d]pyrimidine and Pyrido[3',2':4,5]thieno[3,2-d]-1,2,3-triazin-4-one Derivatives

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CYANOTHIOACETAMIDE IN HETEROCYCLIC SYNTHESIS: A NOVEL SYNTHESIS OF STYRYLPYRIDINETHIONE, STYRYLTHIENO[2,3-b]PYRIDINE, STYRYLPYRAZOLO[3,4-b]PYRIDINE, PYRIDO[2′,3′:3,4]PYRAZOLO[5,1-a]PYRIMIDINE, PYRIDO[3′,2′:4,5]THIENO[3,2-d]PYRIMIDINE AND PYRIDO[3′,2′:4,5]THIENO[3,2-d]-1,2,3-TRIAZIN-4-ONE DERIVATIVES

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Synthesis of 6-styrylpyridinethione ***6a–d****, 6-styrylthienopyridine* ***11a–d****,* ***15a–d****, pyrido[2′,3′:3,4]pyrazolo[5,1-a]pyrimidine* ***25****,* ***29****, pyrido[3′, 2′:4,5]thieno[3,2-d]pyrimidine* ***34****, and pyrido[3′,2′:4,5]thieno[3,2-d]-1,2,3-triazin-4-one* ***35*** *derivatives by the reaction of* ***4a,b****,* ***6a–d****,* ***22****,* ***33****, with* ***5a,b****,* ***9****,* ***13****,* ***23****,* ***27****, acetic anhydride and nitrous acid respectively.*

Keywords: Cyanothioacetamide; pyridopyrazolopyrimidine; pyridoth-Ienotriazinone; styrylpyrazoloopyridine; styrylthienopyridine

The reactivity of 2- and 4-alkylpyridine was studied.[1–3] This phenomenon has found extensive applications.[4–7] In the last decades much attention have been devoted to the construction of new pyridine-2-thione and annelated derivatives on account of their reported biological activities.[8–20] Various series of substituted pyridine-2-thione and their annelated derivatives are reported to have diverse biological activities as antibiotic,[21,22] antiarteriosclerotic,[23] antibacterial,[24] antihyperglycemic,[25] antifungal,[26] agents and as inhibitors of the blood coagulation factor.[27] Also, thienopyridine derivatives have been reported to be useful as antibiotic,[28–31] drug intermediates[32] against endoparasiticides[33] and as antianaphylactics compounds.[34,35] Moreover

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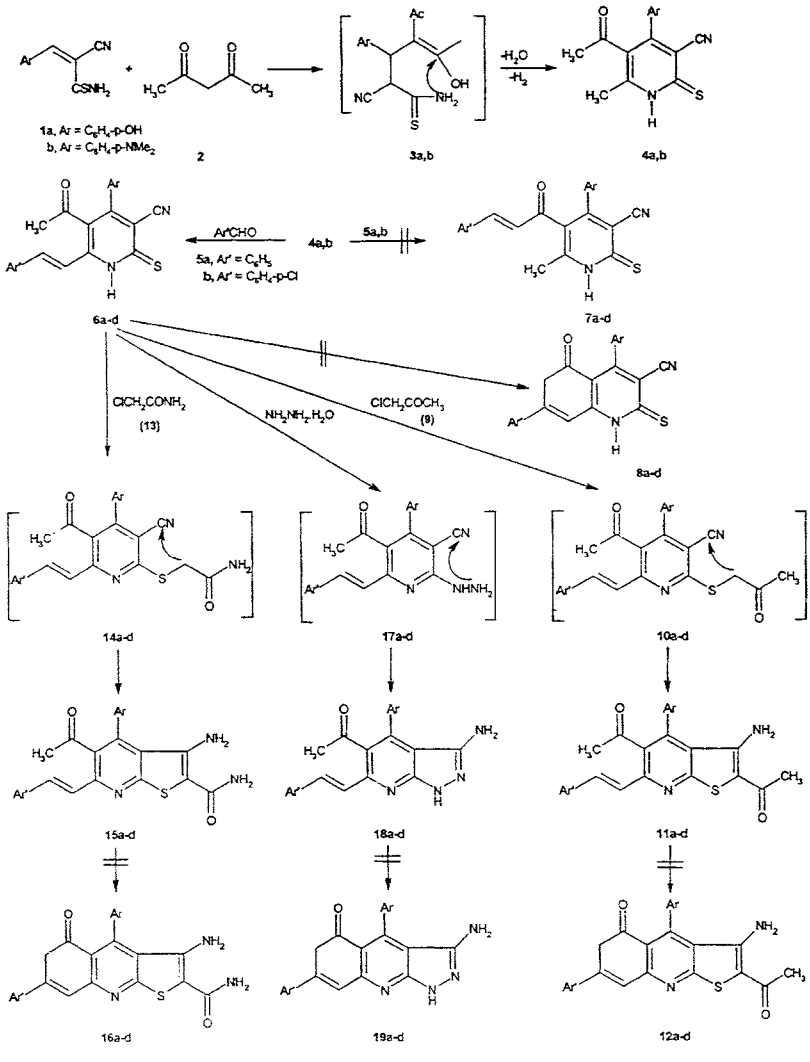
some substituted thienopyridine have been reported to inhibit acetyl CoA-cholesterol O-acetyltransferase[36] the release of cerebal glutamate[37] smooth muscle cells proliferation[38] and the pressor response of angiotensin in rats.[39]

RESULTS AND DISCUSSION

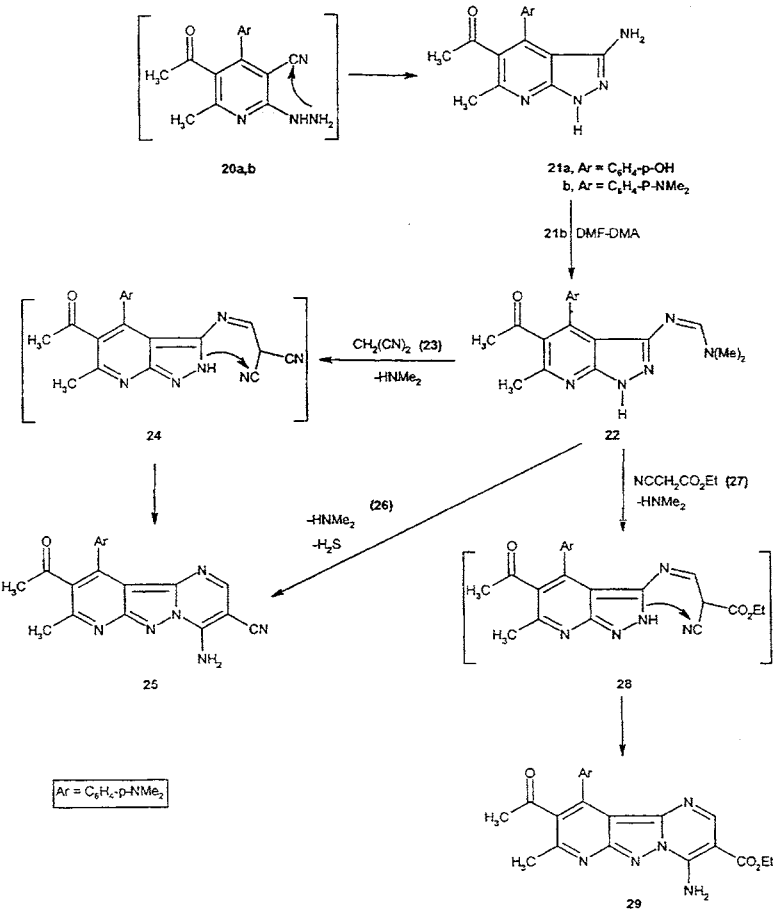
It has been found that compound **1a**,**b** reacted with acetylacetone (**2**) to give the final isolable reaction products **4a**,**b**. Compounds **4a**,**b** could be formed through the non-isolable intermediates **3a**,**b** via the Micheal addition of the methylene group of **2** to the double bond of **1a**,**b** and elimination of one molecule of water and one molecule of hydrogen under the experimental reaction conditions to give the cyclized products **4a**,**b** (cf. Scheme 1). The IR spectrum of **4a** showed the absorption bands of OH, NH, CN, and C=O groups. Moreover its mass spectrum gave the molecular ion peak at 284 which is exactly molecular weight of **4a**. From the above data compound **4a** could be formulated as 5-acetyl-3-cyano-4-(4-hydroxyphenyl)-6-methylpyridine-2-thione (**4a**) (cf. Scheme 1). Due to the reactivity of methyl group at 6 position in pyridine and presence of more than one active site, compounds **4a**,**b** were taking as starting materials for the present work to synthesis a new heterocyclic derivatives with expected biological activity. It has been found that the compound **4a** reacted with benzaldehyde (**5a**) and p-chlorobenzaldehyde (**5b**) to afford the reaction products **6a**,**b** and not **7a–d**.[1–3] The IR spectra of **6a**,**b** showed the absorption bands of nitrile at 2222, carbonyl at 1681. The ^{1}H-NMR of **6a**,**b** revealed the signals of styryl and aromatic protons at 6.83–7.65. Compounds **6a**,**b** could be formed via the condensation reaction between carbonyl group of aldehyde and methyl at pyridine[1–3] ring to give the final isolable reaction product corresponding to 6-styrylpyridine-2-thione derivatives **6a**,**b** (cf. Scheme 1 and Experimental). In the same manner compound **4b** reacted with **5a**,**b** to afford the corresponding 6-styrylpyridinethione **6c**,**d**. These reaction products could be formulated based on the elemental analyses and spectral data as **6a**,**b** previously prepared, all trials to cyclize the compounds **6a–d** into quinolinone-2-thione derivatives **8a–d** are failed. The structure of compounds **6a–d** were confirmed via the reaction of **6a–d** with halogenated compounds such as α-chloroacetone (**9**) and α-chloroacetamide (**13**). It has been found that compound **6a** reacted with chloroacetone (**9**) to yield the corresponding 6-styrylthieno[2,3-b]pyridine derivative **11a**. The IR of **11a** showed the absorption bands at 3201, 3101, and 1697 corresponding to NH_2 and C=O groups at pyridine ring and didn't show any absorption band for nitrile function. Compound **11a** could



6-19	Ar	Ar'
a	C_6H_4-p-OH	C_6H_5
b	C_6H_4-p-OH	C_6H_4-p-Cl
c	C_6H_4-p-NMe_2	C_6H_5
d	C_6H_4-p-NMe_2	C_6H_4-p-Cl

SCHEME 1

be formed via the addition of methylene group to the nitrile function of **10a**. Based on the above data compound **11a** could be formulated as 2,5-diacetyl-3-amino-6-styrylthieno[2,3-b]pyridine derivative. In the same manner compounds **6b–d** reacted with **9** to give the corresponding 6-styrylthieno[2,3-b]pyridine derivatives **11b–d** in respective manner. On the other hand compounds **6a–d** reacted with chloroacetamide (**13**). It has been found that compound **6a** reacted with **13** to give the corresponding 6-styrylthieno[2,3-b]pyridine derivative **15a**. The IR spectrum of **15a** showed the absorption bands of two amino groups at 3373, 3327, 3256, 3192. Moreover it's H-NMR spectrum revealed the signal corresponding to two amino, methyl, aromatic and styryl protons (cf. Experimental Part). In the same manner compounds **6b–d** reacted with **13** and gave the corresponding 6-styrylthieno[2,3-b]pyridine derivative **15b–d** respectively. Compounds **15a–d** were confirmed based on the elemental analyses and spectral data (cf. Scheme I and Experimental). Compounds **6a–d** were further reacted with hydrazine hydrate to give **18a–d**. It has been found that compound **6a** reacted with hydrazine hydrate to afford sulfur free compound corresponding to 6-styrylpyrazolo[3,4–b]pyridine derivative **18a**. The latter reaction product could be formed via the addition of hydrazino group of **17a** to the nitrile function. The IR spectrum of **18a** didn't show any absorption band corresponded to the nitrile function and show the newly born amino group. In the same manner compounds **6b–d** reacted with hydrazine hydrate to give the corresponding 6-styrylpyrazolo[3,4-b]pyridine derivatives **18b–d** respectively. Compounds **18b–d** could be confirmed based on the elemental analyses and spectral data (cf. Scheme 1 and Experimental). All trials to cyclize **11a–d**, **15a–d**, and **18a–d** to the corresponding thieno[2,3-b]qunolinone derivatives and pyrazolo[3,4-b]-quinolinone derivatives **12a–d**, **16a–d** and **19a–d** were unsuccessful. The work was extended to prepare a new heterocyclic derivatives. It has been found that compounds **4a**,**b** reacted with hydrazine hydrate to give the corresponding pyrazolo[3,4-b]pyridine derivatives **21a**,**b**. Compound **21b** was taking as starting material for synthesis new heterocyclic moiety via the reaction with dimethylformamide dimethylacetal (DMF-DMA). It has been found that compound **21b** reacted with dimethylformamide dimethylacetal (DMF-DMA) in dry xylene to afford 3-(N,N-dimethylmethyleneamino)pyrazolo[3,4-b]pyridine derivative **22** (cf. Scheme 2). The IR spectrum of the latter reaction product showed a band at 3179 which corresponded to the NH group in pyrazole ring and didn't show any absorption band corresponding to the amino group which consumed in the reaction to give the imino group. Moreover it's H-NMR spectrum didn't reveal any signal corresponding to the amino group (cf. Scheme 2). Further elucidation of

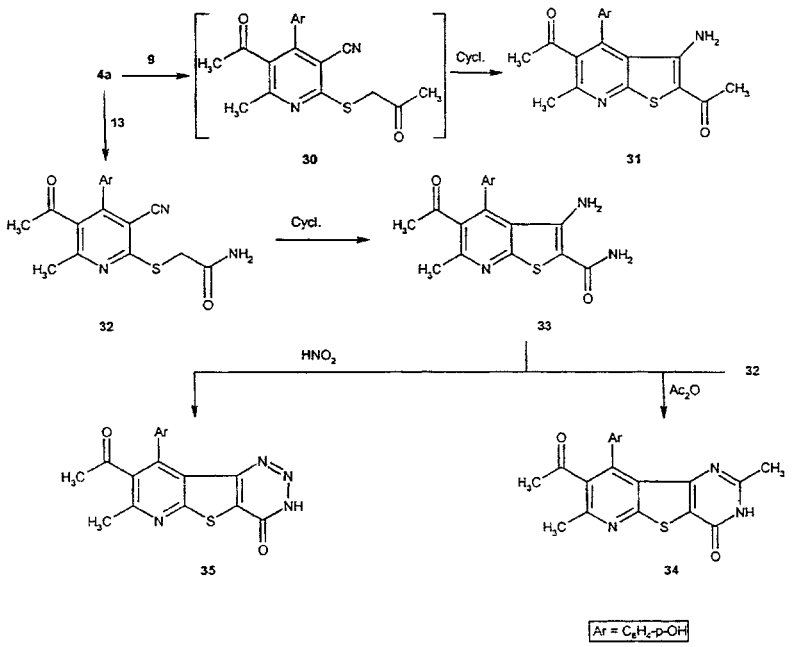


SCHEME 2

compound **22** via the reaction with different active methylene containing compounds such as malononitrile (**23**), cyanothioacetamide (**26**) and ethyl cyanoacetate (**27**). It has been found that compound **22** reacted with **23** to give the corresponding pyrido[2′,3′:3,4]pyrazolo[5,1-a]-pyrimidine derivative **25** via a) loss of one molecule of dimethylamine and b) addition of NH group of pyrazole to the nitrile function in **24**. The IR spectrum of **25** showed the newly born of amino group. Compound **25** could be also prepared via another route by the reaction of **22** with cyanothioacetamide (**26**) to afford the corresponding pyrido-[2′,3′:3,4]pyrazolo[5,1-a]pyrimidine derivative **25** via loss one molecule of dimethylamine and one molecule of hydrogen sulphide. Compound **25** which prepared via this route was found to be identical as **25** previous

prepared in all aspects (melting point and mixed melting point) (cf. Scheme 2 and Experimental).

A third elucidation of compound **22** via its reaction with ethyl cyanoacetate (**27**) to give the corresponding pyrido[2′,3′:3,4]pyrazolo-[5,1-a]pyrimidine derivative **29**. Compound **29** could be confirmed based on the elemental analysis and spectral data (cf. Scheme 2 and Experimental). The work was extended to prepare a new thieno[2,3-b]-pyridine, pyrido[3′2′:4,5]thieno[3,2-d]pyrimidine and pyrido-[3′,2′:4, 5]thieno[3,2-d]-1,2,3-triazin-4-one derivatives. It has been found that compound **4a** reacted with **9** to give the corresponding thieno[2,3-b]pyridine derivative **31**. The IR spectrum of **31** showed the absorption bands at 3468, 3341 which corresponded to the amino group. Moreover it's H-NMR revealed the signal corresponded to the amino protons. Based on the above data compound **31** could be formulated as thieno[2,3-b]pyridine derivative (cf. Scheme 3 and Experimental).



SCHEME 3

On the other hand compound **4a** reacted with **13** to yield the 2-S-carbamoylmethylpyridine derivative **32** which could be cyclized via it's boiling with alcoholic potassium hydroxide solution into thieno[2,3-b]pyridine derivative **33**. Compound **33** could be confirmed via the

reaction with acetic anhydride and nitrous acid to give the corresponding pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine and pyrido[3′,2′:4,5]thieno-[3,2-d]-1,2,3-triazin-4-one derivatives **34** and **35** in respective manner. The structures of compounds **34** and **35** were confirmed based on the elemental analyses and spectral data (cf. Scheme 3 and Experimental). Compound **34** could be synthesized via another route by the reaction of **32** with acetic anhydride to give pyrido[3′,2′:4,5]thieno[3,2-d]-pyrimidine derivative **34**. Compound **34** was formed via this route was found to be identical as **34** previously prepared (cf. Scheme 3 and Experimental).

EXPERIMENTAL

All melting points were measured on a Gallenkamp electrothermal melting point apparatus and are uncorrected. The infrared spectra were recorded in potassium bromide on a Pye Unicam SP 3-300 infrared and FT-IR 8101PC Schimadzu spectrophotometers. The ^{1}H NMR spectra were recorded in deuterated chloroform or dimethyl sulphoxide on a Varian Gemini 200 NMR and varian Mercury 300 MHz spectrometer using tetramethysilane(TMS) as an internal reference; mass spectra were recorded on a GCMS-QP 1000 EX Shimadzu mass spectrumeter at 70 eV. Elemental analysis were carried out at the Microanalytical Center of Cairo University, Giza, Egypt.

Compounds **1a**,**b**,[40] **4b**[13] and **21b**[13] were prepared according to the literature procedure.

Synthesis of Compounds 4a, 6a–d, 25, and 29

General Procedure

A solution of each of **1a**, **4a**,**b**, **22** (0.01 mmol) and **2**, **5a**,**b**, **23** (**26**), **27** (0.01 mmol) in ethanol (30 ml) and piperidine (0.5 ml) were heated under reflux for 5 h. The excess of the ethanol was evaporated in vacuo. The solids obtained were collected by filtration and crystallized from the proper solvent to give **4a**, **6a–d**, **25** and **29** respectively.

*5-Acetyl-3-cyano-4-(4-hydroxyphenyl)-6-methylpyridine-2(1H)-thione (**4a**).* Yellow crystals (75%, ethanol), m.p. 294–296°C; IR (cm^{-1}) ν 3244 (OH), 3101 (NH), 2229 (CN) and 1658 (CO). MS (M = 89.7%, M-15 = 100%). Anal. for $C_{15}H_{12}N_2O_2S$ (284) Calcd: C, 63.36, H, 4.25; N, 9.85; S, 11.28. Found: C, 63.00; H, 4.00; N, 9.60; S, 11.60.

*5-Acetyl-3-cyano-4-(4-hydroxyphenyl)-6-styrylpyridine-2(1H)-thione (**6a**).* Yellow crystals (75% ethanol), m.p. 226–228°C; IR (cm^{-1}) ν 3425

(OH), 3417 (NH), 2222 (CN), 1682 (C=O). Anal. for $C_{22}H_{16}N_2O_2S$ (372.45) Calcd: C, 70.95; H, 4.33; N, 7.52; S, 8.61. Found: C, 71.10; H, 4.10; N, 7.90; S, 8.70.

*5-Acetyl-3-cyano-4-(4-hydroxyphenyl)-6-(4-chlorostyryl)pyridine-2-(1H)-thione (**6b**).* Yellow crystals (80%, ethanol), m.p. 182–184°C; IR (cm^{-1}) ν 3420 (OH), 3209 (NH), 2206 (CN), 1682 (C=O); ^{1}H NMR (DMSO) δ 1.78 (s, 3H, CH_3), 4.36 (brs, 1H, NH), 6.83–7.65 (m, 10H, ArH's and CH=CH) and 7.73 (s, 1H, OH). Anal. for $C_{22}H_{15}N_2O_2SCl$ (406.89) Calcd: C, 64.94; H, 3.72; N, 6.88; S, 7.88; Cl, 8.71. Found: C, 64.60; H, 3.90; N, 6.70; S, 8.10.

*5-Acetyl-3-cyano-4-(4-N,N-dimethylaminophenyl)-6-styrylpyridine-2(1H)-thione (**6c**).* Yellow crystals (75%, ethanol), m.p. 234–236°C; IR (cm^{-1}) ν 3230, (NH), 2210 (CN); 1678 (C=O); MS (M = 100%, M-15 = 31.1%). Anal. for $C_{24}H_{21}N_3OS$ (399.52) Calcd: C, 72.15; H, 5.30; N, 10.52; S, 8.03. Found: C, 72.40; H, 4.10; N, 10.50; S, 7.90.

*5-Acetyl-3-cyano-4-(4-N,N-dimethylaminophenyl)-6-(4-chlorostyryl)-pyridine-2(1H)-thione (**6d**).* Brown crystals (80%, ethanol), m.p. 282–284°C; IR (cm^{-1}) ν 3417 (NH), 2214 (CN), 1697 (C=O). Anal. for $C_{24}H_{20}N_3OSCl$ (433.96) Calcd: C, 66.43; H, 4.65; N, 9.68; S, 3.69; Cl, 8.17. Found: C, 66.30; H, 4.80; N, 9.90; S, 3.80; Cl, 8.30.

*9-Acetyl-4-amino-8-methyl-10-(4-N,N-dimethylaminophenyl)pyrido-[2′,3′:3,4]pyrazolo-[5,1-a]pyrimidine-3-carbonitrile (**25**).* Pale-green crystals (75%, ethanol), m.p. >350°C; IR (cm^{-1}) ν 3433, 3271 (NH_2), 2214 (CN); 1682 (C=O); MS (M = 98.04%, M-15 = 100%). Anal. for $C_{21}H_{19}N_7O$. (385.43) Calcd: C, 65.44; H, 4.97; N, 25.44. Found: C, 65.30; H, 4.80; N, 25.70.

*Ethyl-9-acetyl-4-amino-8-methyl-10-(4-N,N-dimethylaminophenyl)-pyrido[2′,3′:3,4]-pyrazolo[5,1-a]pyrimidine-3-carboxylate (**29**).* Yellow crystals (75%, ethanol), m.p. 308–310°C; IR (cm^{-1}) ν 3402, 3232 (NH_2), 1689 (C=O); ^{1}HNMR ($CDCl_3$) d 1.37–1.44 (t, 3H, $OCH_2\underline{CH_3}$), 1.64 (s, 2H, NH_2), 1.98 (s, 3H, CH_3 at pyridine), 2.70 (s, 3H, $COCH_3$), 3.07 (s, 6H, $N(Me)_2$), 4.37–4.48 (q, 2H, $O\underline{CH_2}CH_3$) 6.78–7.53 (m, 4H, ArH's) and 8.91 (s, 1H, CH at pyrimidine). Anal. for $C_{23}H_{24}N_6O_3$ (432.00) Calcd: C, 63.88; H, 5.59; N, 19.43. Found: C, 63.60; H, 5.80; N, 19.50.

Synthesis of Compounds 11a–d and 31

General Procedure

A solution of each of **6a–d** and **4a** (0.01 mmol) in sodium ethoxide (0.01 mmol) prepared from 0.01 mmol sodium metal in 30 ml ethanol) and chloroacetone (**9**) (0.01 mmol) was heated under reflux for 5 h. Cool

poured on to ice bath, then acidified with hydrochloric acid. The solid products were collected by filtration, washed with water and crystallized from the proper solvent to give **11a–d** and **31** respectively.

*2,5-Diacetyl-3-amino-4-(4-hydroxyphenyl)-6-styrylthieno[2,3-b]pyridine (**11a**).* White crystals (60% ethanol/DMF), m.p. >330°C; IR (cm^{-1}) ν 3417 (OH), 3201, 3101 (NH_2), 1705, 1674 (two C=O). Anal. for $C_{25}H_{20}N_2O_3S$ (428.51) Calcd: C, 70.07; H, 4.70; N, 6.54; S, 7.48. Found: C, 70.20; H, 4.50; N, 6.40; S, 7.20.

*2,5-Diacetyl-3-amino-4-(4-hydroxyphenyl)-6-(4-chlorostyryl)thieno[2,3-b]pyridine (**11b**).* Yellow crystal (60% ethanol), m.p. 308–310°C; IR (cm^{-1}) ν 3471 (OH), 3310, 3125 (NH_2), 1705 (C=O). ^1H NMR (DMSO) δ 2.1 (s, 3H, $COCH_3$ at pyridine), 2.38 (s, 3H, $COCH_3$ at thiophene), 3.58 (s, 2H, NH_2), 6.95–7.99 (m, 10H, ArH's and CH=CH) and 10.1 (s, 1H, OH). Anal. for $C_{25}H_{19}N_2O_3SCl$ (462.96) Calcd: C, 64.86; H, 4.14; N, 6.05; S, 6.93; Cl, 7.66. Found: C, 64.70; H, 4.30; N, 6.3; S, 7.10; Cl, 7.30.

*2,5-Diacetyl-3-amino-4-(4-N,N-dimethylaminophenyl)-6-styrylthieno-[2,3-b]pyridine (**11c**).* Orange crystals (55% ethanol), m.p. 281–283°C; IR (cm^{-1}) 3464, 3320 (NH_2), 1705 (C=O); ^1H NMR (DMSO) δ 2.1 (s, 3H, $COCH_3$ at pyridine), 2.38 (s, 3H, $COCH_3$ at thiophene), 3.37 (s, 6H, $N(CH_3)_2$), 6.51 (brs, 2H, NH_2) and 6.85–8.00 (m, 11H, ArH's and CH=CH). Anal. for $C_{27}H_{25}N_3O_2S$ (455.58) Calcd: C, 71.18; H, 5.53; N, 9.22; S, 7.04. Found: C, 71.20; H, 5.30; N, 9.5; S, 7.30.

*2,5-Diacetyl-3-amino-4-(4-N,N-dimethylaminophenyl)-6-(4-chlorostyryl)thieno[2,3-b]pyridine (**11d**).* Brown crystals (60% ethanol), m.p. >340°C; IR (cm^{-1}) ν 3425, 3351 (NH_2), 1702 (C=O). Anal. for $C_{27}H_{24}N_3O_2SCl$ (490.03) Calcd: C, 66.18; H, 4.94; N, 8.58; S, 6.54; Cl, 7.23. Found: C, 66.30; H, 4.70; N, 8.70; S, 6.80; Cl, 6.90.

*2,5-Diacetyl-3-amino-4-(4-hydroxyphenyl)-6-methylthieno[2,3-b]pyridine (**31**).* Yellow crystals (60% ethanol), m.p. 308–310°C; IR (cm^{-1}) ν 3500 (OH), 3468, 3341 (NH_2), 1697, 1632 (two C=O). ^1H NMR (DMSO) δ 2.00 (s, 3H, $COCH_3$ at pyridine), 2.35 (s, 3H, $COCH_3$ at thiophene), 6.46 (brs, 2H, NH_2) 6.97–7.21 (m, 4H, ArH's) and 10.34 (s, 1H, OH). Anal. For. $C_{18}H_{16}N_2O_3S$ (340.40) Calcd: C, 63.51; H, 4.74; N, 8.23; S, 942. Found: C, 63.40; H, 4.90; N 8.50; S, 9.20.

Synthesis of 15a–d and 32

General Procedure

A solution of each of **6a–d** and **4a** (0.01 mmol) in sodium ethoxide (0.01 mmol prepared from 0.01 mmol sodium metal in 30 ml ethanol)

and chloroacetamide (**13**) (0.01 mmol) was heated under reflux for 5 h. It was cooled by being poured into an ice-bath, then acidified with hydrochloric acid. The solid products were collected by filtration, washed with water, and crystallized from the proper solvent to give **15a–d** and **32** respectively.

*5-Acetyl-3-amino-2-carbamoyl-4-(4-hydroxypyenyl)-6-styrylthieno[2,3-b]pyridine (**15a**).* Yellow crystals (65%, ethanol), m.p. 256–258°C; IR (cm^{-1}) ν 3483 (OH), 3373, 3327, 3250, 3192 (two NH_2), 1697, 1654 (two C=O); ^1H NMR (DMSO) δ 2.01 (s, 3H, $COCH_3$), 4.1 (s , 2H, NH_2), 6.94-8.22 (m, 13H, ArH's, NH_2 and CH=CH) and 7.88 (s, 1H, OH). MS (M = 80.2%, M-18 = 30.9%, M-44 = 100%). Anal. for $C_{24}H_{19}N_3O_3S$ (429.50) Calcd: C, 67.12; H, 4.46; N, 9.78; S, 7.47. Found: C, 67.1; H, 4.2; N, 10.00; S, 7.40.

*5-Acetyl-3-amino-2-carbamoyl-4-(4-hydroxypyenyl)-6-(4-chlorostyryl)-thieno[2,3-b]pyridine (**15b**).* Brown crystals (55%, ethanol), m.p. 319–321°C; IR (cm^{-1}) ν 3483 (OH), 3373, 3327, 3250, 3192 (two NH_2), 1697, 1654 (two C=O). Anal. for $C_{24}H_{18}N_3O_3SCl$ (463.95) Calcd: C, 62.13; H, 3.91; N, 9.06; S, 6.91; Cl, 7.64. Found: C, 62.30; H, 4.00; N, 9.20; S, 6.70; Cl, 7.30.

*5-Acetyl-3-amino-2-carbamoyl-4-(4-N,N-dimethylaminopyenyl)-6-styrylthieno[2,3-b]pyridine (**15c**).* Yellow crystals (65%, ethanol), m.p. 312–314°C; IR (cm^{-1}) ν 3472, 3356, 3210, 3180 (two NH_2), 1690 (C=O); ^1H NMR ($CDCl_3$) δ 1.95 (s, 3H, $COCH_3$), 3.96 (s , 2H, NH_2), 3.05 (s, 6H, $N(Me)_2$) and 6.74–8.16 (m, 13H, ArH's, NH_2 and CH=CH). Anal. for $C_{26}H_{24}N_4O_2S$ (456.57) Calcd: C, 68.40; H, 5.30; N, 12.27; S, 7.02. Found: C, 68.10; H, 5.6; N, 13.00; S, 7.30.

*5-Acetyl-3-amino-2-carbamoyl-4-(4-N,N-dimethylaminophyenyl)-6-(4-chlorostyryl)thieno[2,3-b]pyridine (**15d**).* Brown crystals (60%, ethanol), m.p. >330°C; IR (cm^{-1}) ν 3460, 3350, 3220, 3190 (two NH_2) 1688 (two C=O). Anal. for $C_{26}H_{23}N_4O_2SCl$ (491.02) Calcd: C, 63.60; H, 4.72; N, 11.41; S, 6.53; Cl, 7.22. Found: C, 63.50; H, 4.50; N, 11.20; S, 6.20; Cl, 7.00.

*5-Acetyl-2-carbamoylmethylthio-3-cyano-4-(4-hydroxyphenyl)-6-methylpyridine (**32**).* Yellow crystals (70%, ethanol), m.p. 226–228°C; IR (cm^{-1}) ν 3456 (OH), 3364, 3295 (NH_2), 2222 (CN), 1682 (C=O); ^1H NMR (DMSO) δ 1.98 (s, 3H, CH_3), 2.53 (s, 3H, $COCH_3$), 4.1 (s, 2H, $S\underline{CH_2}CONH_2$), 6.98–7.28 (m, 4H, ArH's), 7.77 (s, 1H, OH), 10.2 (brs, 4H, two NH_2). Anal. for $C_{17}H_{15}N_3O_3S$ (341.39) Calcd: C, 59.81; H, 4.43; N, 12.31; S, 9.39. Found: C, 59.00; H, 4.70; N, 12.20; S, 9.50.

Synthesis of 18a–d and 21a

A solution of each of **6a–d** and **4a** (0.01 mmol) in hydrazine hydrate (5 ml) and ethanol (20 ml) was heated under reflux for 5 h. The solid products that formed were collected by filtration and crystallized from the proper solvent to give **18a–d** and **21a** respectively.

*5-Acetyl-3-amino-4-(4-hydroxyphenyl)-6-styrylpyrazolo[3,4-b]pyridine (**18a**).* Brown crystals (70%, dilute ethanol), m.p. 201–203°C; IR (cm^{-1}) ν 3460 (OH), 3364, 3294, 3217 (NH_2 and NH), 1690 (C=O). Anal. for $C_{22}H_{18}N_4O_2$ (370.41) Calcd; C, 71.34; H, 4.90; N, 15.13. Found: C, 71.50, H, 4.80; N, 15.3.

*5-Acetyl-3-amino-4-(4-hydroxyphenyl)-6-(4-chlorostyryl)pyrazolo[3,4-b]pyridine (**18b**).* Brown (70%, dilute ethanol), m.p. 203–205°C; IR (cm^{-1}) ν 3460 (OH), 3430, 3294, 3194 (NH_2 and NH), 1682 (C=O). ^1H NMR (DMSO) δ 1.58 (s, 2H, NH_2), 1.93 (s, 3H, $COCH_3$), 6.71–7.23 (m, 10H, ArH's and CH=CH), 7.44 (s, 1H, OH) and 9.54 (s, 1H, NH). Anal. for $C_{22}H_{17}N_4O_2Cl$ (404.86) Calcd: C, 65.27; H, 4.23; N, 13.84; Cl, 8.76. Found: C, 65.50; H, 4.50; N, 14.00; Cl, 8.60.

*5-Acetyl-3-amino-4-(4-N,N-dimethylaminophenyl)-6-styrylpyrazolo-[3,4-b]pyridine (**18c**).* Yellow crystals (70%, ethanol), m.p. 276–278°C, IR (cm^{-1}) ν 3425, 3310, 3140 (NH_2 and NH) (C=O). ^1H NMR ($CDCl_3$) δ 1.78 (s, 3H, $COCH_3$), 2.98 (s, 6H, $N(Me)_2$), 5.79 (brs, 1H, NH), 6.71–7.39 (m, 13H, ArH's, NH_2 and CH=CH). Anal. for $C_{24}H_{23}N_5O$ (397.48) Calcd: C, 72.52; H, 5.83; N, 17.62. Found: C, 72.50; H, 6.00; N, 17.90.

*5-Acetyl-3-amino-4-(4-N,N-dimethylaminophenyl)-6-(4-chlorostyryl)-pyrazolo[3,4-b]pyridine (**18d**).* Yellow (70%, dilute ethanol), m.p. 280–282°C; IR (cm^{-1}) ν 3456, 3302, 3194 (NH_2 and NH) (1689 (C=O). ^1H NMR (DMSO) δ 1.94 (s, 3H, $COCH_3$), 3.00 (s, 6H, NMe_2), 4.45 (s, 2H, NH_2), 6.85–7.21 (m, 10H, ArH's and CH=CH) and 12.21 (s, 1H, NH). Anal. for $C_{24}H_{22}N_5OCl$ (431.93) Calcd: C, 66.74; H, 5.13; N, 16.21; Cl, 8.21. Found: C, 66.50; H, 4.80; N, 15.90; Cl, 8.50.

*5-Acetyl-3-amino-4-(4-hydroxyphenyl)-6-methylpyrazolo[3,4-b]pyridine (**21a**).* Yellow (70%, ethanol), m.p. 310–312°C; IR (cm^{-1}) ν 3460 (OH), 3294, 3194 (NH_2 and NH), 1683 (C=O). Anal. for $C_{15}H_{14}N_4O_2$ (282.3) Calcd: C, 63.82 H, 5.00; N, 19.85. Found: C, 63.50, H, 4.80; N, 20.00.

Synthesis of 22

A solution of **4b** (0.01 mmol) and dimethylformamide dimethylacetal (DMF-DMA 0.01 mmol) in dry xylene (30 ml) was heated under reflux

for 4 h. The excess of xylene evaporated in vacuo. The residue was triturated with petroleum ether the solid obtained was collected by filtration and crystallized from ethanol to give **22**.

*5-Acetyl-4-(4-N,N-dimethylaminophenyl)-6-methyl-3-(N,N-dimethylaminomethyleneamino)pyrazolo[3,4-b]pyridine (**22**).* Yellow (70%, ethanol), m.p. 248–250°C; IR (cm^{-1}) ν 3179 (NH) 1690 (C=O); ^1H NMR (DMSO) δ 1.90 (s, 3H, CH_3), 2.72 (s, 3H, $COCH_3$), 2.93 (s, 6H, NMe_2), 2.97 (s, 6H, NMe_2), 6.74–7.23 (m, 4H, ArH's), 7.72 (s, 1H, $N=\underline{CH}-NMe_2$) and 12.60 (s, 1H, NH) Anal. for $C_{20}H_{24}N_6O$ (364.45) Calcd: C, 65.91 H, 6.64; N, 23.06. Found: C, 66.00; H, 6.40; N, 22.90.

Synthesis of 33

A solution of **32** (1 mmol), potassium hydroxide (2 mmol) and ethanol (30 ml) was heated under reflux for 4 h. It was cooled and acidified with concentrated hydrochloric acid. The solid obtained was collected by filtration and crystallized from ethanol to give **33**.

*5-Acetyl-3-amino-2-carbmoyl-4-(4-hydroxyphenyl)-6-methylthieno[2,3-b]pyridine (**33**).* Yellow crystals (75% ethanol), m.p. 255–257°C; IR (cm^{-1}) ν OH (3417), 3390, 3280 (two NH_2), 1682, 1643 (two C=O). Anal. For. $C_{17}H_{15}N_3O_3S$ (341.39) Calcd: C, 59.81; H, 4.43; N, 12.31; S, 9.39. Found: C, 60.00; H, 4.70; N, 12.20; S, 9.50.

Synthesis of 34

A solution of **32** or **33** (0.01 mmol) in acetic anhydride (20 ml) was heated under reflux for 4 h. The solid obtained was collected by filtration and crystallized from acetic acid to give **34**.

*8-Acetyl-2,7-dimethyl-9-(4-hydroxyphenyl)pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4-one (**34**).* White crystals (55%, acetic acid), m.p. 328–330°C; IR (cm^{-1}) ν 3448 (OH), 3385 (NH), 1705, 1651 (two C=O). Anal. for $C_{19}H_{15}N_3O_3S$ (365) Calcd: C, 62.45; H, 4.14; N, 11.50; S, 8.77. Found: C, 62.40; H, 3.90; N, 11.20; S, 9.90.

Synthesis of 35

To a stirred cold solution (0–5°C) of **33** (1 mmol) in water (10 ml) and concentrated hydrochloric acid (5 ml), a solution of sodium nitrite (0.23 g in 5 ml of water) was added during 30 min. Stirring was continued for 40 min at −5°C. The reaction mixture was then allowed to stand at 0–5°C for 3 h. The solid obtained was collected by filtration and crystallized from ethanol to give **35**.

*7-Acetyl-8-methyl-9-(4-hydroxyphenyl)pyrido[3′,2′:4,5]thieno[3,2-d]-1,2,3-triazin-4-one (**35**)*. Yellow crystals (55%, ethanol), m.p. >320°C; IR (cm^{-1}) ν 3418 (OH), 3320 (NH), 1697, 1651 (two C=O). Anal. for $C_{17}H_{12}N_4O_3S$ (352.37) Calcd: C, 57.95; H, 3.43; N, 15.90; S, 9.10. Found: C, 58.10; H, 3.70; N,16.10; S, 8.90.

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