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Synthesis of Dihydropyridine, Alkylthiopyridine, Thienopyridine and Pyridothienopyrimidine Derivatives

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The reaction of arylidene cyanothioacetamide (**1a,b**) with acetylacetone (**2**) gave dihydropyridine derivatives (**3a,b**). Compounds (**3a,b**) on reaction with some halogenated derivatives (**5A-C**) to afford 2-alkylthiopyridine derivatives (**6-8**). The compounds (**3a,b**) reacted with (**5A-G**) to give thieno[2,3-b]pyridine derivatives (**9-13**). The compounds (**9, 10**) reacted with formic acid, (**9**) with formamide, and (**10**) with acetic anhydride to give (**14-16**), respectively.

Key Words: Synthesis, Dihydropyridine, Alkythiopyridine, Thienopyridine, Pyridothienopyrimidine.

INTRODUCTION

Recently a number of researchers are concerned with the synthesis of new dihydrothioxopyridine derivatives (**3a,b**) and annelated pyridine derivatives has gained our attention due to the biological activities of thienopyridine derivatives as antibacterial[1-3], antihypertensive[4], antimicrobial[5], pyridothienopyrimidine derivatives as antipyretics[6] and antiinflammatories[7,8].

EXPERIMENTAL

All melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. The infrared spectra were recorded on a Pye Unicam SP 3-300 and Shimadzu FT IR 8101 PC infrared spectrophotometers (KBr disks). The ^{1}H NMR and ^{13}C NMR spectra were recorded in dimethyl sulphoxide (DMSO-d_6) at 300 MHz on a Varian Mercury VX-300 NMR spectrometer using TMS as internal reference. Electron impact mass spectra were run on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 e.v. Elemental analyses were carried out at the Microanalytical

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Center of Cairo University, Giza, Egypt. Arylidene cyanothioacetamide derivatives (**1a,b**) were prepared as described in the literature[9,10].

Synthesis of thioxo-1,2-dihydropyridine-3-carbonitrile derivatives (3a,b)

Method A: A mixture of each of (**1a,b**) (0.01 mol) and acetylacetone (**2**) (0.01mol) in dioxane (30 mL) containing a catalytic amount of piperidine (0.3 mL) was refluxed for 4 h. Then, the reaction mixture was evaporated and cooled. The precipitated solid was collected, washed with ethanol and crystallized from ethanol to give (**3a,b**).

Method B: A ternary mixture of cyanothioacetamide (**1**), acetylacetone (**2**) and each of aromatic aldehydes (0.01 mol) in dioxane (30 mL) containing a catalytic amount of piperidine (0.3mL), was heated under reflux for 4-5 h. The reaction mixture was evaporated and the crude product was collected, washed with ethanol and crystallized from ethanol to give (**3a,b**).

5-Acetyl-4-(benzo[1,3]dioxo-5-yl)-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (3a): It was crystallized from ethanol as yellow crystals (75%); m.p. 270-2°C; IR (KBr, cm^{-1}) 3184 ν(NH), 2229 ν(CN) and 1693 ν(CO acetyl) cm^{-1}; ^1H NMR (δ) 1.83 (s, 3H, pyridine CH_3), 2.34 (s, 3H, $COCH_3$), 6.14 (s, 2H, OCH_2O), 7.04-7.31 (m, 3H, ArH's) and 13.2 (s, br., 1H, NH) ppm; MS: m/z = 312. Anal. for $C_{16}H_{12}N_2O_3S$ Calcd. (Found) %: C 61.53 (61.62), H 3.84 (3.71), N 8.97 (8.72), S 10.25 (10.03).

5-Acetyl-4-(3,4-dimethoxyphenyl)-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (3b): It was crystallized from ethanol as yellow crystals (69%); m.p. 240-2°C; IR (KBr, cm^{-1}) 3193 ν(NH), 2231 ν(CN) and 1691 ν(CO acetyl) cm^{-1}; ^1H NMR (δ) 1.80 (s, 3H, pyridine CH_3), 2.37 (s, 3H, $COCH_3$), 3.77 and 3.84 (s,s 6H, two OCH_3), 6.89-7.12 (m, 3H, ArH's) and 14.10 (s, br., 1H, NH) ppm; MS: m/z = 328. Anal. for $C_{17}H_{16}N_2O_3S$ Calcd. (Found) %: C 62.19 (61.33), H 4.87 (5.02), N 8.53 (8.43), S 9.76 (9.54).

Synthesis of 2-alkylthiopyridine-3-carbonitrile derivatives: A solution of each of (**3a,b**) (0.01 mol) in ethanolic sodium ethoxide solution [prepared from sodium metal (0.2 g, 0.01 g atom) and absolute ethanol (30 mL)], was treated with each of the reagents (**5A-C**) (0.01 mol). The reaction mixture was stirred for 2-3 h. The solid formed was collected, washed with cold ethanol and then crystallized from the ethanol to give (**6a,b**); (**7a,b**); and (**8a,b**), respectively.

2-[5-Acetyl-4-(benzo[1,3]dioxo-5-yl)-3-cyano-6-methylpyrid-2-yl]thioacetonitrile (6a): It was crystallized from ethanol as yellow crystals (84%); m.p. 170-72°C; IR (KBr, cm^{-1}) 2223, 2221 ν(CN), 1697 ν(CO acetyl) cm^{-1}; ^1H NMR (δ) 2.02 (s, 3H, pyridine CH_3), 2.55 (s, 3H, $COCH_3$), 3.91 (s, 2H, CH_2CN), 6.13 (s, 2H, OCH_2O) and 6.81-7.23 (m, 3H, ArH's) ppm; MS: m/z = 351. Anal. for $C_{18}H_{13}N_3O_4S$ Calcd. (Found) %: C 61.54 (61.20), H 3.70 (3.55), N 11.96 (11.91), S 9.11 (8.70).

2-[5-Acetyl-3-cyano-4-(3,4-dimethoxyphenyl)-6-methylpyrid-2-yl]thioacetonitrile (6b): It was crystallized from ethanol as yellow crystals (78%); m.p.165-67°C; IR (KBr, cm^{-1}) 2224, 2221 ν(CN), 1699 ν(CO acetyl) cm^{-1}; ^1H NMR (δ) 2.06 (s, 3H, pyridine CH_3), 2.53 (s, 3H, $COCH_3$), 3.71 and 3.82 (s,s, 6H, two OCH_3), 3.93 (s, 2H, CH_2) and 6.94-7.25 (m, 3H, ArH's) ppm; MS: m/z = 367. Anal. for $C_{19}H_{17}N_3O_3S$ Calcd. (Found) %: C 62.12 (62.01), H 4.63 (4.62), N 11.44 (11.40), S 8.71 (8.60).

5-Acetyl-4-(benzo[1,3]dioxo-5-yl)-2-(carbamoylmethylthio)-6-methyl-pyridine-3-carbonitrile (7a): It was crystallized from ethanol as yellow crystals (83%); m.p. 198-200°C; IR (KBr, cm^{-1}) 3430, 3355 (ν)(NH_2), 2223 ν(CN), 1690 ν(CO acetyl), 1598 ν(CO amide) cm^{-1}; ^1H NMR (δ) 1.98 (s, 3H, pyridine CH_3), 2.45 (s, 3H, $COCH_3$), 3.99 (s, 2H, SCH_2), 6.13 (s, 2H, OCH_2O), 6.99-7.15 (m, 3H, ArH's) and 6.78, 7.61 (s,s, 2H, NH_2) ppm; ^{13}C NMR (δ) 203.1 ($COCH_3$), 168.8 ($CONH_2$), 114.9 (CN), 102.0 (OCH_2O), 33.9 ($COCH_3$), 31.6 (SCH_2) and 23.2 (CH_3 pyridine) ppm, in addition of aromatic carbon atoms; MS: m/z = 369. Anal. for $C_{18}H_{15}N_3O_4S$ Calcd. (Found) %: C 58.53 (58.43), H 4.06 (4.12), N 11.38 (11.0), S 8.67 (8.60).

5-Acetyl-2-(carbamoylmethylthio)-4-(3,4-dimethoxyphenyl)-6-methyl-pyridine-3-carbonitrile (7b): It was crystallized from ethanol as yellow crystals (76%); m.p.178-80°C; IR (KBr, cm^{-1}) 3455, 3306 ν(NH_2), 2221 ν(CN), 1699 ν(CO acetyl), 1595 ν(CO amide) cm^{-1}; ^1H NMR (δ) 1.97 (s, 3H, pyridine CH_3), 2.42 (s, 3H, $COCH_3$), 3.77 and 3.84 (s,s, 6H, two OCH_3), 6.96-7.13 (m, 3H, ArH's) and 6.74, 7.54 (s,s, 2H, NH_2) ppm; MS: m/z = 385. Anal. for $C_{19}H_{19}N_3O_4S$ Calcd. (Found) %: C 59.22 (58.90), H 4.93 (4.87), N 10.9 (10.5), S 8.34 (8.32).

Ethyl 2-[5-acetyl-4-(benzo[1,3]dioxo-5-yl)-3-cyano-6-methylpyrid-2-yl]- thioacetate (8a): It was crystallized from ethanol as yellow crystals (68%); m.p.150-52°C; IR (KBr, cm^{-1}) 2221 ν(CN), 1745 ν(CO ester), 1695 ν(CO acetyl) cm^{-1}; ^1H NMR (δ) 1.23 (t, 3H, $COOCH_2CH_3$), 2.04 (s, 3H, pyridine CH_3), 2.54 (s, 3H, $COCH_3$), 4.21 (q, 2H, $COOCH_2CH_3$), 6.13 (s, 2H, OCH_2O) and 6.82-7.09 (m, 3H, ArH's) ppm; MS: m/z = 398. Anal. for $C_{20}H_{18}N_2O_5S$ Calcd. (Found) %: C 60.30 (60.25), H 4.52 (4.50), N 7.03 (6.94), S 8.04 (8.02).

Ethyl 2-[5-acetyl-4-(3,4-dimethoxyphenyl)-3-cyano-6-methylpyrid-2-yl] thioacetate (8b): It was crystallized from ethanol as yellow crystals (76%); m.p. 143-45°C; IR (KBr, cm^{-1}) 2221 ν(CN), 1748 ν(CO ester), 1699 ν(CO acetyl) cm^{-1}; ^1H NMR (δ) 1.22 (t, 3H, $COOCH_2CH_3$), 2.11 (s, 3H, pyridine CH_3), 2.67 (s, 3H, $COCH_3$), 3.77 and 3.84 (s,s 3H, two OCH_3), 4.13 (q, 2H, $COOCH_2CH_3$) and 6.84-7.04 (m, 3H, ArH's) ppm; MS: m/z = 414. Anal. for $C_{21}H_{22}N_2O_5S$ Calcd. (Found) %: C 60.87 (60.85), H 5.31 (5.25), N 6.76 (6.72), S 7.73 (7.55).

Synthesis of 3-aminothieno[2,3-b]pyridine derivatives (9-13a,b): A solution of each of (**3a,b**) (0.01 mol) in ethanol containing 10% potassium hydroxide solution, was treated with (**5A-G**) (0.01 mol). The reaction mixture was refluxed for 2-3 h. After cooling, the reaction mixture was poured in ice-cold water (50 mL). The solid formed was collected, washed with cold ethanol and then crystallized from the ethanol to give (**9-13a,b**). The compounds obtained were listed below with their physical data.

5-Acetyl-3-amino-4-(benzo[1,3]dioxo-5-yl)-6-methylthieno[2,3-b]pyridine-2-carbonitrile (9a): It was crystallized from ethanol as yellow crystals (81%); m.p. 275-77°C; IR (KBr, cm^{-1}) 3366, 3074 ν(NH$_2$), 2220 ν(CN), 1691 ν(CO acetyl) cm^{-1}; ^{1}H NMR (δ) 2.03 (s, 3H, pyridine CH$_3$), 2.55 (s, 3H, COCH$_3$), 4.41 (s, br., 2H, NH$_2$), 6.14 (s, 2H, OCH$_2$O) and 6.85-7.22 (m, 3H, ArH's) ppm; MS: m/z= 351. Anal. for $C_{18}H_{13}N_3O_4S$ Calcd. (Found) %: C 61.54 (61.2), H 3.70 (3.55), N 11.96 (11.91), S 9.11 (8.70).

5-Acetyl-3-amino-4-(3,4-dimethoxyphenyl)-6-methylthieno[2,3-b]pyridine-2-carbonitrile (9b): It was crystallized from ethanol as yellow crystals (76%); m.p.255-58°C; IR (KBr, cm^{-1}) 3366, 3075 ν(NH$_2$), 2221 ν(CN), 1693 ν(CO acetyl) cm^{-1}; ^{1}H NMR (δ) 2.06 (s, 3H, pyridine CH$_3$), 2.5 (s, 3H, COCH$_3$), 3.77 and 3.84 (s,s, 6H, two OCH$_3$), 4.42 (s, br., 2H, NH$_2$) and 6.83-7.08 (m, 3H, ArH's) ppm; MS: m/z = 367. Anal. for $C_{19}H_{17}N_3O_3S$ Calcd. (Found) %: C 62.12 (61.97), H 4.63 (4.52), N 11.44 (11.42), S 8.71 (8.55).

5-Acetyl-3-amino-4-(benzo[1,3]dioxo-5-yl)-6-methylthieno[2,3-b]pyridine-2-carboxamide (10a): It was crystallized from ethanol as yellow crystals (81%); m.p. 225-27°C; IR (KBr, cm^{-1}) 3455, 3306, 3274 ν(two NH$_2$), 1699 ν(CO acetyl), 1674 ν(CO amide) cm^{-1}; ^{1}H NMR (δ) 2.06 (s, 3H, pyridine CH$_3$), 2.49 (s, 3H, COCH$_3$), 6.13 (s, 2H, OCH$_2$O), 5.82 (s, br., 2H, NH$_2$), 6.79-6.95 (m, 3H, ArH's) and 7.16 (s, br., 2H, CONH$_2$) ppm; ^{13}C NMR (δ) 204.7 (COCH$_3$), 166.9 (CONH$_2$), 101.8 (OCH$_2$O), 32.3 (COCH$_3$) and 22.8 (CH$_3$ pyridine) ppm, in addition of absorption bands of aromatic carbon atoms; MS: m/z = 369. Anal. for $C_{18}H_{15}N_3O_4S$ Calcd. (Found) %: C 58.53 (58.43), H 4.06 (4.12), N 11.38 (11.0), S 8.67 (8.60).

5-Acetyl-3-amino-4-(3,4-dimethoxyphenyl)-6-methylthieno[2,3-b]pyridine-2-carboxamide (10b): It was crystallized from ethanol as yellow crystals (76%); m.p.210-12°C; IR (KBr, cm^{-1}) 3460, 3373, 3294 ν(two NH$_2$), 1700 ν(CO acetyl), 1641ν(CO amide) cm^{-1}; ^{1}H NMR (δ) 2.06 (s, 3H, pyridine CH$_3$), 2.5 (s, 3H, COCH$_3$), 3.77 and 3.84 (s,s, 6H, two OCH$_3$), 5.82 (s, br., 2H, NH$_2$), 6.78-7.05 (m, 3H, ArH's) and 7.14 (s, br., 2H, CONH$_2$) ppm; MS: m/z = 385. Anal. for $C_{19}H_{19}N_3O_4S$ Calcd. (Found) %: C 59.22 (59.20), H 4.93 (4.83), N 10.9 (10.2), S 8.34 (8.30).

Ethyl 5-acetyl-3-amino-4-(benzo[1,3]dioxo-5-yl)-6-methylthieno [2,3-b]-pyridine-2-carboxylate (11a): It was crystallized from ethanol as yellow crystals (68%); m.p. 265-67°C. IR (KBr, cm^{-1}) 3455, 3306 $\nu(NH_2)$, 1723 ν(CO ester), 1699 ν(CO acetyl) cm^{-1}. ^1H NMR (δ) 1.21 (t, 3H, $COOCH_2CH_3$), 2.06 (s, 3H, pyridine CH_3), 2.54 (s, 3H, $COCH_3$), 4.01 (q, 2H, $COOCH_2CH_3$), 5.74 (s, br., 2H, NH_2), 6.14 (s, 2H, OCH_2O) and 6.82-7.07 (m, 3H, ArH's) ppm. ^{13}C NMR (δ) 204.5 ($COCH_3$), 164.4 (CO ester), 101.9 (OCH_2O), 32.2 ($COCH_3$), 22.8 (CH_3 pyridine) and 14.4 (CH_3 ester) ppm, in addition of aromatic carbon atoms. MS: m/z = 398. Anal. for $C_{20}H_{18}N_2O_5S$ Calcd. (Found) %: C 60.30 (60.34), H 4.52 (4.51), N 7.03 (6.88), S 8.04 (8.02).

Ethyl-5-acetyl-3-amino-4-(3,4-dimethoxyphenyl)-6-methylthieno [2,3-b]-pyridine-2-carboxylate (11b): It was crystallized from ethanol as yellow crystals (76%); m.p. 250-52°C; IR (KBr, cm^{-1}) 3455, 3306 $\nu(NH_2)$, 1718 ν(CO ester), 1699 ν(CO acetyl) cm^{-1}; ^1H NMR (δ) 1.23 (t, 3H, $COOCH_2CH_3$), 2.11 (s, 3H, pyridine CH_3), 2.67 (s, 3H, $COCH_3$), 3.77 and 3.84 (s,s, 6H, two OCH_3), 4.10 (q, 2H, $COOCH_2CH_3$), 6.01 (s, br., 2H, NH_2) and 6.84-7.06 (m, 3H, ArH's) ppm; MS: m/z = 414. Anal. for $C_{21}H_{22}N_2O_5S$ Calcd. (Found) %: C 60.87 (60.75), H 5.31 (5.20), N 6.76 (6.60), S 7.73 (7.30).

1-[3-Amino-4-(benzo[1,3]dioxo-5-yl)-2-benzoyl-6-methylthieno [2,3-b]-pyrid-5-yl]ethanone (12a): It was crystallized from ethanol as yellow crystals (81%); m.p. 225-7°C; IR (KBr, cm^{-1}) 3460, 3321 $\nu(NH_2)$, 1699 ν(CO acetyl) cm^{-1}; ^1H NMR(δ) 2.06 (s, 3H, pyridine CH_3), 3.25 (s, 3H, $COCH_3$), 6.14 (s, 2H, OCH_2O), 6.4 (s, br., 2H, NH_2), 6.8-7.2 (m, 3H, ArH's) and 7.5-7.7 (m, 5H, phenyl) ppm; MS: m/z = 430. Anal. for $C_{24}H_{18}N_2O_4S$ Calcd. (Found) %: C 66.97 (66.70) H 4.18 (4.09), N 6.51 (6.30), S 7.44 (7.30).

1-[3-Amino-2-benzoyl-4-(3,4-dimethoxyphenyl)-6-methylthieno [2,3-b]-pyrid-5-yl]ethanone (12b): It was crystallized from ethanol as yellow crystals (76%); m.p.230-2°C; IR (KBr, cm^{-1}) 3463, 3324 $\nu(NH_2)$, 1703 ν(CO acetyl) cm^{-1}; ^1H NMR (δ) 2.04 (s, 3H, pyridine CH_3), 3.23 (s, 3H, $COCH_3$), 3.78 and 3.86 (s,s, 6H, two OCH_3), 6.53 (s, br., 2H, NH_2), 6.83-7.22 (m, 3H, ArH's) and 7.52-7.75 (m, 5H, phenyl) ppm; MS: m/z = 446. Anal. for $C_{25}H_{22}N_2O_4S$ Calcd. (Found) %: C 67.26 (67.18), H 4.93 (4.91), N 6.27 (6.11), S 7.17 (7.00).

1-[5-Acetyl-3-amino-4-(benzo[1,3]dioxo-5-yl)-6-methylthieno[2,3-b]pyrid-2-yl]ethanone (13a): It was crystallized from ethanol as yellow crystals (81%); m.p. 225-7°C; IR (KBr, cm^{-1}) 3455, 3306 $\nu(NH_2)$, 1699 ν(CO acetyl) cm^{-1}; ^1H NMR (δ) 2.06 (s, 3H, pyridine CH_3), 2.50 (s, 6H, two $COCH_3$), 6.13 (s, 2H, OCH_2O), 6.46 (s, br., 2H, NH_2) and 6.81-7.08 (m, 3H, ArH's) ppm.; ^{13}C NMR(δ) 204.4 ($COCH_3$), 191.8 ($COCH_3$), 101.2

(OCH_2O), 32.3 ($COCH_3$), 29.2 ($COCH_3$) and 22.9 (CH_3 pyridine) ppm, in addition of aromatic carbon atoms; MS: m/z = 368. Anal. for $C_{19}H_{16}N_2O_4S$ Calcd. (Found) %: C 61.95 (61.68), H 4.34 (4.31), N 7.60 (7.39), S 8.70 (8.50).

1-[5-Acetyl-3-amino-4-(3,4-dimethoxyphenyl)-6-methylthieno[2,3-b]pyrid-2-yl]ethanone (13b): It was crystallized from ethanol as yellow crystals (76%); m.p. 210-2°C; IR (KBr, cm^{-1}) 3445, 3320 $\nu(NH_2)$, 1699 ν(CO acetyl) cm^{-1}; ^1H NMR (δ) 2.06 (s, 3H, pyridine CH_3), 2.51 (s, 6H, $COCH_3$), 3.77 and 3.84 (s,s, 6H, OCH_3), 6.52 (s, br., 2H, NH_2) and 6.81-7.06 (m, 3H, ArH's) ppm; MS: m/z = 384. Anal. for $C_{20}H_{20}N_2O_4S$ Calcd. (Found) %: C 62.48 (62.36), H 5.24 (5.10), N 7.29 (7.25), S 8.34 (8.20).

Synthesis of 15a,b; 16a,b and 17a,b: (General method): A solution of each of 9a,b or 10a,b; (0.01 mol each) in formic acid, formamide and acetic anhydride (20 mL each) was refluxed for 4 h. The reaction mixture was cooled. The product so formed was collected, washed with cold ethanol and crystallized from ethanol to (14-16) respectively.

8-Acetyl-9-(benzo[1,3]dioxo-5-yl)-7-methyl-3,4-dihydropyrid-[3',2':4,5]-thieno[3,2-d]pyrimidine-4-one (14a): It was crystallized from ethanol as yellow crystals (81%); m.p. > 320°C; IR (KBr, cm^{-1}) 3159 ν(NH), 1696 ν(CO acetyl), 1669 ν(CO pyrimidine) cm^{-1}; ^1H NMR (δ) 2.04 (s, 3H, pyridine CH_3), 2.52 (s, 3H, $COCH_3$), 6.13 (s, 2H, OCH_2O), 6.84-6.92 (m, 3H, ArH's), 7.93 (s, 1H, pyrimidine H) and 8.09 (s, 1H, NH) ppm; MS: m/z = 379. Anal. for $C_{19}H_{13}N_3O_4S$ Calcd. (Found) %: C 60.15 (60.13), H 3.43 (3.32), N 11.08 (10.93), S 8.44 (8.40).

8-Acetyl-9-(3,4-dimethoxyphenyl)-7-methyl-3,4-dihydropyrido [3`,2`:4,5]-thieno[3,2-d]pyrimidin-4-one (14b): It was crystallized from ethanol as yellow crystals (75%); m.p. > 310°C; IR (KBr, cm^{-1}) 3157 ν(NH), 1693 ν(CO acetyl), 1665 ν(CO pyrimidine) cm^{-1}; ^1H NMR (δ) 1.98 (s, 3H, pyridine CH_3), 2.48 (s, 3H, $COCH_3$), 3.76 and 3.87 (s,s, 6H, two OCH_3), 6.8-7.2 (m, 3H, ArH's), 7.92 (s, 1H, pyrimidine H) and 8.11 (s, 1H, NH) ppm; MS: m/z = 395. Anal. for $C_{20}H_{17}N_3O_4S$ Calcd. (Found) %: C 60.76 (60.44), H 4.30 (4.25), N 10.63 (10.44), S 8.10 (7.96).

1-[4-Amino-9-(benzo[1,3]dioxo-5-yl)-7-methylpyrido[3`,2`:4,5] thieno[3,2-d]pyrimid-8-yl] ethanone (15a): It was crystallized from ethanol as yellow crystals (87%); m.p. 290-92°C; IR (KBr, cm^{-1}) 3330, 3180 $\nu(NH_2)$, 1696 ν(CO acetyl) cm^{-1}; ^1H NMR (δ) 2.13 (s, 3H, pyridine CH_3), 2.57 (s, 3H, $COCH_3$), 6.14 (s, 2H, OCH_2O), 6.85-7.13 (m, 3H, ArH's), 7.95 (s, 1H, pyrimidine H) and 12.8 (s, br., 2H, NH_2) ppm; MS: m/z = 378. Anal. for $C_{19}H_{14}N_4O_3S$ Calcd. (Found) %: C 60.31 (60.24) H 3.70 (3.63), N 14.81 (14.73) S 8.46 (8.25).

1-[4-Amino-9-(3,4-dimethoxyphenyl)-7-methylpyrido[3`,2`:4,5]-thieno[3,2-d]pyrimid-8-yl]ethanone (15b): It was crystallized from ethanol as yellow crystals (76%); m.p. 283-85°C; IR (KBr, cm^{-1}) 3455, 3306 ν(NH_2), 1699 ν(CO acetyl) cm^{-1}; ^1H NMR (δ) 1.96 (s, 3H, pyridine CH_3), 2.56 (s, 3H, $COCH_3$), 3.70 and 3.83 (s,s, 6H, two OCH_3), 6.78-7.03 (m, 3H, ArH's), 8.23 (s, 1H, pyrimidine H) and 12.78 (s, br., 2H, NH_2) ppm; MS: m/z = 394. Anal. for $C_{20}H_{18}N_4O_3S$ Calcd. (Found) %: C 60.91 (60.70), H 4.56 (4.50), N 14.20 (14.00), S 8.13 (8.11).

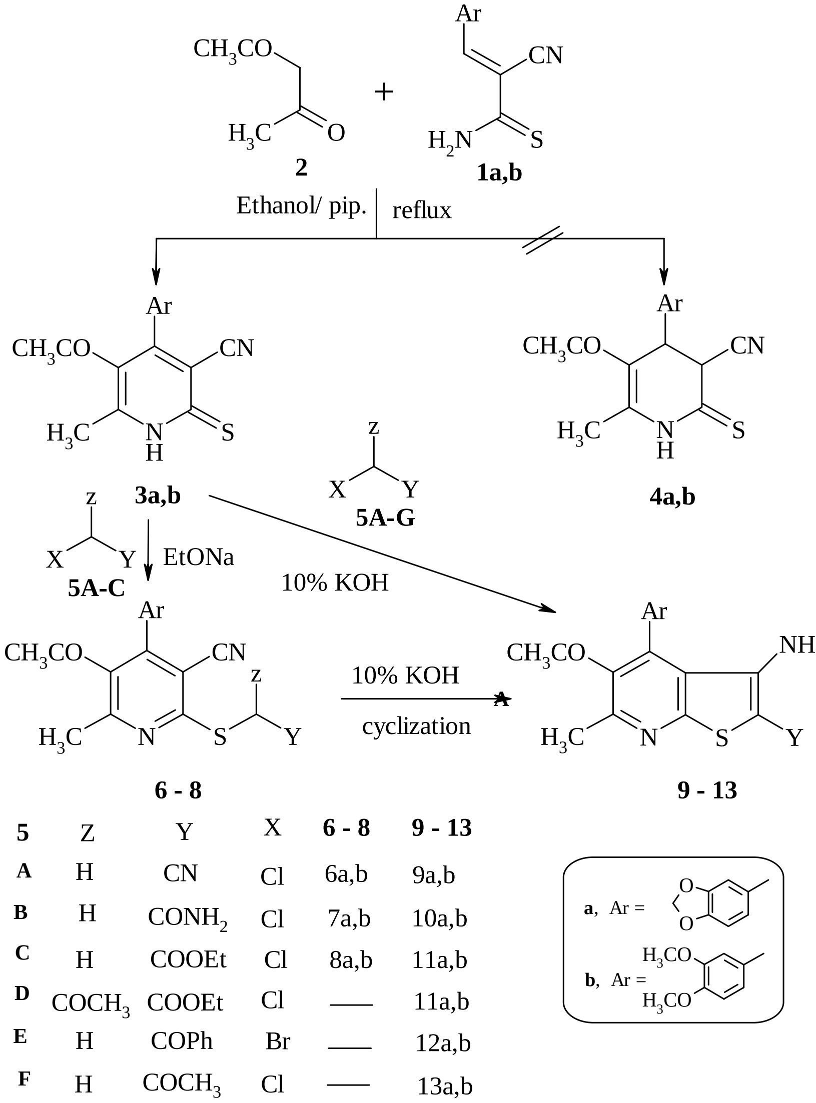
8-Acetyl-9-benzo[1,3]dioxo-5-yl-2,7-dimethyl-3,4-dihydropyrido [3`,2`:4,5]thieno[3,2-d]pyrimidin-4-one (16a): It was crystallized from ethanol as yellow crystals (80%); m.p. 292-94°C; IR (KBr, cm^{-1}) 3160 ν(NH), 1699 ν(CO acetyl), 1660 ν(CO pyrimidine) cm^{-1}; ^1H NMR (δ) 1.83 (s, 3H, pyrimidine CH_3), 2.14 (s, 3H, pyridine CH_3), 2.61 (s, 3H, $COCH_3$), 6.14 (s, 2H, OCH_2O), 7.01-7.25 (m, 3H, ArH's) and 12.5 (s, 1H, NH) ppm; MS: m/z = 393. Anal. for $C_{20}H_{15}N_3O_4S$ Calcd. (Found) %: C 61.06 (61.03), H 3.81 (3.63), N 10.68 (10.52), S 8.14 (8.10).

8-Acetyl-9-(3,4-dimethoxyphenyl)-2,7-dimethyl-3,4-dihydropyrido [3`,2`:4,5]thieno[3,2-d]pyrimidin-4-one (16b): It was crystallized from ethanol as yellow crystals (72%); m.p. 285-87°C; IR (KBr, cm^{-1}) 3160, ν(NH_2), 1696 ν(CO acetyl), 1655 ν(CO pyrimidine) cm^{-1}; ^1H NMR (δ) 1.95 (s, 3H, pyrimidine CH_3), 2.12 (s, 3H, pyridine CH_3), 2.54 (s, 3H, $COCH_3$), 3.70 and 3.81 (s,s, 6H, two OCH_3), 6.78-6.95 (m, 3H, ArH's) and 12.69 (s, 1H, NH) ppm; MS: m/z = 409. Anal. for $C_{21}H_{19}N_3O_4S$ Calcd. (Found) %: C 61.61 (61.54), H 4.64 (4.62), N 10.26 (10.23), S 8.82 (8.30).

RESULT AND DISCUSSION

Arylidene cyanothioacetamide (**1**) has been reported to react with acetylacetone (**2**) to give either a mixture of dihydro-2-thioxopyridine derivatives (**3**) with tetrahydro-2-thioxopyridine derivatives (**4**)[5,11,12], or (**3**) as the only product[13]. In our laboratory, the reaction of different derivatives of (**1a,b**) with acetylacetone (**2**) in boiling dioxane containing a catalytic amount of piperidine afford the corresponding (**3a,b**) and the structure of (**4a,b**) was excluded on the basis of elemental analysis and spectral data. As an example, the ^1H NMR shows no signals at δ 4.1(d), 4.4(d) ppm corresponding to the H(4) and H(3) of the tetrahydropyridine derivatives (**4b**)[12] and revealed a signal at δ 14.1 ppm for the NH proton, in addition to the protons of pyridine substituents. Furthermore, its mass spectrum gave m/z = 328, which correspond to the molecular formula of the assigned structure $C_{17}H_{16}N_2O_3S$. Compounds (**3a,b**) were used as good synthons to synthesize thienopyridine and pyridothino-pyrimidine derivatives. Thus, (**3a,b**) were reacted with halogeno active methylene compounds (**5a-c**) in ethanolic sodium ethoxide solution to yield the corresponding

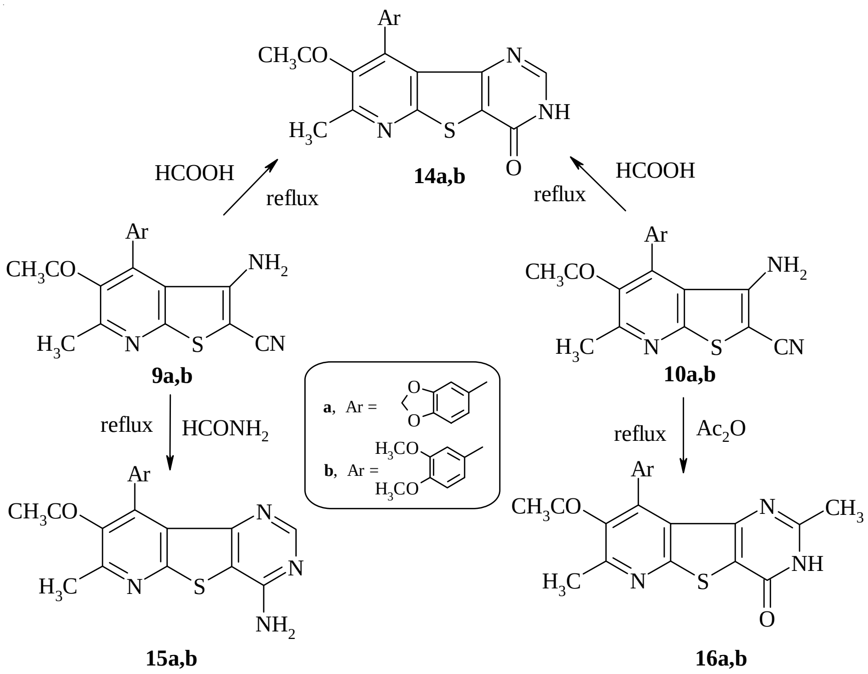
2-alkylthiopyridine-3-carbonitrile derivatives (**6-8**) (**Scheme-1**). The structures of the products (**6-8**) were inferred from their elemental analyses and spectral data (experimental part). Thus, the IR spectrum of (**7a**) as an example lacked band due to (C=S) group, but shows bands near 3430, 3355 ν(NH_2), 2223 ν(CN), 1690 ν(acetyl CO) and 1598 ν(amide CO) cm^{-1}. ^1H NMR spectrum of (**7a**) contains a singlet signal at δ 3.99 ppm (SCH_2), two singlet signals corresponding to amidic NH_2 protons at δ 6.78 and 7.61 ppm. Also ^{13}C NMR and the mass spectra were compatible with the structure. Also, the reaction of (**3a,b**) with (**5A-G**) in refluxing ethanolic



5	Z	Y	X	6 - 8	9 - 13
A	H	CN	Cl	6a,b	9a,b
B	H	$CONH_2$	Cl	7a,b	10a,b
C	H	COOEt	Cl	8a,b	11a,b
D	$COCH_3$	COOEt	Cl	—	11a,b
E	H	COPh	Br	—	12a,b
F	H	$COCH_3$	Cl	—	13a,b
G	$COCH_3$	$COCH_3$	Cl	—	13a,b

Scheme 1

10 % KOH solution gave, in each case, a single compound as evidenced by TLC analysis of the crude reaction product. The products were identified as 3-aminothieno[2,3-b]pyridine derivatives (**9-13**), respectively (**Scheme 1**) resulting from nucleophilic substitution reaction followed by intramolecular addition to the nitrile group. The structure of the latter compounds was assigned on the basis of elemental analyses and spectral data. Thus, the infrared spectra of all formed compounds contain bands of new formed amino group near 3400, 3300 cm^{-1}, in addition to the bands for the remainder groups of the structure. ^1H NMR spectrum of (**11b**), as an example, exhibits a singlet signal at δ 6.0 ppm corresponds to the new formed NH_2 protons. The mass spectrum showed a correct molecular weight m/z = 414 for the molecular formula $C_{21}H_{22}N_2O_2S$ for (**11b**). The structure of (**9-11**) were further confirmed by their alternative synthesis. Thus, refluxing of (**6-8**) in ethanolic 10% KOH solution gave compound identical in all respect, physical & spectral data, with those of compound (**9-11**), respectively (**Scheme 1**) mentioned that the products formed from the reaction of (**3a,b**) with each of (**5C,D**) and (**5F,G**) were identical in all respects, physical and spectral data, and assigned as (**11a,b**); (**13a,b**), respectively.



Scheme 2

Further confirmation of structures of (**9,10**) was achieved through refluxing of (**9,10**) in formic acid, (**9**) in formamide and (**10**) in acetic anhydride. The compounds formed were formulated as pyrido[3,2:4,5]thieno

[3,2-d]pyrimidinone (**14a,b**), aminopyrido[3,2:4,5]-thieno[3,2-d]pyrimidine (**15a,b**) and methyl pyrido[3,2:4,5]thieno[3,2-d]pyrimidinone (**16a,b**) respectively (**Scheme-2**). The products formed (**14-16**) were inferred through their correct elemental analyses and spectral data. Thus, ^{1}H NMR spectra of compound (**14**) reveal the absence of a signal at δ 4.41 for NH_2 protons of the corresponding **9** and at δ 7.16 for $CONH_2$ protons of the corresponding (**10**) and the appearance of a singlet at 7.92 for pyrimidine H and a singlet at δ 8.11 for NH proton. Also, the spectral data of the compound (**15, 16**) are compatible of the proposed structures.

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