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Synthesis and Characterization of Thioxopyridine, Pyrazolopyridine and Pyridopyrazolotriazine Derivatives

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Derivatives of arylidene cyanothioacetamide (**4a,b**) reacted with ethyl acetoacetate to give the thioxopyridine derivatives (**6a,b**). Compounds **6a,b** reacted with methyl iodide to yield methylthiopyridine derivatives (**7a,b**). Hydrazine hydrate reacted with either **6a,b** or **7a,b** to give aminopyrazolopyridine derivatives (**8a,b**). The diazonium salts of **8a,b** reacted with several active methylene compounds **1, 10a-h** to afford the pyridopyrazolotriazine derivatives (**11-19a,b**), respectively.

Key Words: Cyanothioacetamide, Thioxopyridines, Methylthiopyridines, Pyrazolo-[3,4-b]pyridines, Pyrido[2, 3:3,4]pyrazolo-[5,1-c]triazines.

INTRODUCTION

Significant work have been done using cyanothioacetamide derivatives[1-6] in the synthesis of thioxopyridine and its annelated derivatives of considerable biological activities[7-11]. These findings aspired us to resume these efforts using new derivatives of cyanothioacetamide to synthesize thioxopyridine, pyrazolopyridine and pyridopyrazolotriazine derivatives compounds.

EXPERIMENTAL

Melting points were taken on a gallenkamp apparatus and are uncorrected. Infrared spectra (KBr) were determined on a Pye Unicam SP-300 and Shimadzu FT IR 8101 PC infrared spectrophotometers. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were determined on a Varian Mercury VX NMR spectrometer in DMSO with TMS as the internal standard. Mass spectra were recorded on a GCMS-QP 1000 EX Shimadzu, Japan. Elemental analyses were carried out at the Microanalytical center of the university of Cairo, Giza, Egypt.

Arylidene cyanothioacetamide (**4a**,**b**) were prepared[12,13] as previously described.

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Preparation of dihydro-6-thioxopyridine derivatives (6a,b)

Method A: A mixture of each of **4a,b** (0.01 mol) and the equivalent amount of ethyl acetoacetate (0.01 mol) in dioxane (30 mL) containing a catalytic amount of piperidine (0.3 mL) was heated under reflux for 6 h as indicated by TLC analysis. The solvent was evaporated and the solid that formed was collected by filtration and crystallized from ethanol to give **6a,b**.

Method B: A ternary mixture of cyanothioacetamide, ethyl acetoacetate and the appropriate aromatic aldehyde (0.01 mol) in dioxane (30 mL) containing a catalytic amount of piperidine (0.3 mL) was heated under reflux for 6 h as indicated by TLC analysis. The solvent was evaporated and the solid that formed was collected by filtration and crystallized from ethanol to give **6a,b**.

Ethyl 4-(1,3-benzodioxol-5-yl)-5-cyano-2-methyl-6-thioxo-1,6-dihydropyridine-3-carboxylate (6a): Yellow crystals; IR (ν_{max}): 3458 (NH), 2226 (CN), 1708 (CO ester) cm^{-1}; ^1H NMR (δ): 2.49 (t, *J* = 6.9 Hz, 3H, $COOCH_2\mathbf{CH_3}$), 3.28 (s, 3H, CH_3 pyridine), 3.93 (q, *J* = 6.9 Hz, 2H, $COO\mathbf{CH_2}CH_3$), 6.10 (s, 2H, OCH_2O), 6.78-7.03 (m, 3H, ArH's), 13.9 (s, br., 1H, NH) ppm; ^{13}C NMR (δ): 178.6 (C = S), 164.6 ($\mathbf{COO}CH_2CH_3$), 116 (CN), 154.5-108.2 (10 aromatic carbon atoms), 101.8 (OCH_2O), 61.5 ($COO\mathbf{CH_2}CH_3$), 18.0 (CH_3 pyridine) and 13.5 ($COOCH_2\mathbf{CH_3}$) ppm.

Ethyl 5-cyano-4-(3,4-dimethoxyphenyl)-2-methyl-6-thioxo-1,6-dihydropyridine-3-carboxylate (6b): Yellow crystals; IR (ν_{max}): 3446 (NH), 2227 (CN), 1708 (CO ester) cm^{-1}; ^1H NMR (δ): 2.39 (t, *J* = 6.9 Hz, 3H, $COOCH_2\mathbf{CH_3}$), 3.15 (s, 3H, CH_3 pyridine), 3.77, 3.82 (two s, 6H, two OCH_3), 3.93 (q, *J* = 6.9 Hz, 2H, $COO\mathbf{CH_2}CH_3$), 6.89-7.12 (m, 3H, ArH's), 14.10 (s, br., 1H, NH) ppm.

Preparation of 6-methylthiopyridine derivatives (7a,b): A solution of each **6a,b** (0.01 mol) and methyl iodide (0.01 mol) in methanolic sodium methoxide (0.01 mol) was stirred at room temperature for 3 h. The reaction mixture was poured into 50 mL of water. The solid that formed was collected, washed with cold ethanol and crystallized from ethanol to afford **7a,b**.

Ethyl 4-(1,3-benzodioxol-5-yl)-5-cyano-2-methyl-6-methylthiopyridine-3-carboxylate (7a):

White crystals; IR (ν_{max}): 2223 (CN), 1737 (CO ester) cm^{-1}; ^1H NMR (δ): 0.95 (t, *J* = 6.9 Hz, 3H, $COOCH_2\mathbf{CH_3}$), 2.55 (s, 3H, CH_3 pyridine), 2.7 (s, 3H, SCH_3), 4.06 (q, *J* = 6.9 Hz, 2H, $COO\mathbf{CH_2}CH_3$), 6.11 (s, 2H, OCH_2O), 6.81-7.05 (m, 3H, ArH's) ppm; ^{13}C NMR (δ): 166.2 ($\mathbf{COO}CH_2CH_3$), 114.8 (CN), 163.3-104.5 (11 aromatic C's), 101.8 (OCH_2O), 61.6 ($COO\mathbf{CH_2}CH_3$), 23.38 (CH_3 pyridine), 13.62 (SCH_3), 13.07 ($COOCH_2\mathbf{CH_3}$) ppm.

Ethyl 5-cyano-4-(3,4-dimethoxyphenyl)-2-methyl-6-methylthiopyridine-3-carboxylate (7b): White crystals; IR (ν_{max}): 2221 (CN), 1730 (CO ester) cm^{-1}; ^1H NMR (δ): 0.96 (t, J = 6.9 Hz, 3H, $COOCH_2\mathbf{CH_3}$), 2.57 (s, 3H, CH_3 pyridine), 2.66 (s, 3H, SCH_3), 3.77, 3.83 (two s, 6H, two OCH_3), 4.08 (q, J = 6.9 Hz, 2H, $COO\mathbf{CH_2}CH_3$), 6.91-7.10 (m, 3H, ArH's) ppm.

Preparation of 3-aminopyrazolo[3,4-b]pyridine derivatives (8a,b): To a solution of each of **6a,b** or **7a,b** (0.01 mol) in absolute ethanol (10 mL), hydrazine hydrate (20 mL) was added. The mixture was heated under reflux for 6-7 h. The product formed after cooling was filtered, washed with cold ethanol and crystallized from ethanol to give **8a,b**.

Ethyl 3-amino-4-(1,3-benzodioxol-5-yl)-6-methyl-1H-pyrazolo-[3,4-b]pyridine-5-carboxylate (8a): Yellow crystals; IR (ν_{max}): 3453, 3287, 3156 (NH, NH_2), 1715 (CO ester) cm^{-1}; ^1H NMR (δ): 0.95 (t, J = 6.9 Hz, 3H, $COOCH_2\mathbf{CH_3}$), 2.50 (s, 3H, CH_3 pyridine), 4.02 (q, J = 6.9 Hz, 2H, $COO\mathbf{CH_2}CH_3$), 4.41 (s, 2H, NH_2), 6.10 (s, 2H, OCH_2O), 6.77-7.04 (m, 3H, ArH's), 12.26 (s, 1H, NH) ppm; ^{13}C NMR (δ): 168.4 ($\mathbf{COO}CH_2CH_3$), 154.6-108.4 (12 aromatic C's), 101.6 (OCH_2O), 60.8 ($COOCH_2\mathbf{CH_3}$), 23.3 (CH_3 pyridine), 13.7 ($COOCH_2\mathbf{CH_3}$) ppm.

Ethyl 3-amino-4-(3,4-dimethoxyphenyl)-6-methyl-1H-pyrazolo-[3,4-b]Pyridine-5-carboxylate (8b): Yellow crystals; IR (ν_{max}): 3443, 3293, 3190 (NH, NH_2), 1722 (CO ester) cm^{-1}; ^1H NMR (δ): 0.95 (t, J = 6.9 Hz, 3H, $COOCH_2\mathbf{CH_3}$), 2.53 (s, 3H, CH_3 pyridine), 3.77, 3.83 (two s, 6H, two OCH_3), 4.09 (q, J = 6.9 Hz, 2H, $COO\mathbf{CH_2}CH_3$), 4.31 (s, 2H, NH_2), 6.88-7.11 (m, 3H, ArH's), 12.15 (s, 1H, NH) ppm.

General preparation of pyrido[2,3:3,4]pyrazolo[5,1-c]triazine derivatives (11-19): To a cold solution of **8a,b** (0.01 mol) in ethanol (20 mL) and hydrochloric acid (3 mL) was added dropwise a cold aqueous sodium nitrite solution (0.01 mol) with stirring. After complete addition, stirring was continued for 2 h in an ice chest. The diazonium salts formed was filtered, washed with cold water and then with ethanol. A solution of the prepared diazonium salts and the appropriate active methylene compounds **1**, **10a-h** (0.01 mol) in ethanol (30 mL) was heated under reflux in the presence of piperidine (0.3 mL) for 3 h, or was stirred in the presence of sodium acetate for 4 h. The product formed in either case, was filtered, washed with cold ethanol and crystallized from the proper solvent to give **11-19a,b**, respectively.

Ethyl 4-amino-10-(1,3-benzodioxol-5-yl)-8-methyl-3-thioaminocarbonylpyrido[2,3:3,4]pyrazolo[5,1-c][1,2,4]triazine-9-carboxylate (11a): Yellow crystals; IR (ν_{max}): 3484, 3446, 3293, 3149 (two NH_2), 1710 (CO ester) cm^{-1}; ^1H NMR (δ): 1.07 (t, J = 6.9 Hz, 3H, $COOCH_2\mathbf{CH_3}$), 2.70 (s, 3H, CH_3 pyridine), 4.16 (q, J = 6.9 Hz, 2H, $COO\mathbf{CH_2}CH_3$), 6.12 (s, 2H, OCH_2O), 7.01-7.18 (m, 3H, ArH's), 9.51, 9.89, 10.22, 10.70 (4s, 4H, two NH_2) ppm.

Ethyl 4-amino-10-(3,4-dimethoxyphenyl)-8-methyl-3-thioaminocarbonylpyrido[2,3:3,4]pyrazolo[5,1-c][1,2,4]triazine-9-carboxylate (11b): Yellow crystals; IR (ν_{max}): 3480, 3442, 3290, 3145 (two NH_2), 1710 (CO ester) cm^{-1}; ^1H NMR (δ): 1.05 (t, *J* = 6.9 Hz, 3H, $COOCH_2\mathbf{CH_3}$), 2.60 (s, 3H, CH_3 pyridine), 3.70, 3.82 (two s, 6H, two OCH_3), 4.13 (q, *J* = 6.9 Hz, 2H, $COO\mathbf{CH_2}CH_3$), 6.99-7.20 (m, 3H, ArH's), 9.48, 9.85, 10.21, 10.67 (4s, 4H, two NH_2) ppm.

Ethyl 4-amino-10-(1,3-benzodioxol-5-yl)-3-cyano-8-methylpyrido-[2,3:3,4]pyrazolo[5,1-c][1,2,4]triazine-9-carboxylate (12a): Yellow crystals; IR (ν_{max}): 3292, 3190 (NH_2), 2227 (CN), 1722 (CO ester) cm^{-1}; ^1H NMR (δ): 1.01 (t, *J* = 6.9 Hz, 3H, $COOCH_2\mathbf{CH_3}$), 2.67 (s, 3H, CH_3 pyridine), 4.20 (q, *J* = 6.9 Hz, 2H, $COO\mathbf{CH_2}CH_3$), 6.17 (s, 2H, OCH_2O), 6.90-7.20 (m, 3H, ArH's), 9.82 (s, br., 2H, NH_2); ^{13}C NMR (δ): 167.9 ($\mathbf{COO}CH_2CH_3$), 115.4 (CN), 161.1-102.4 (14 aromatic C's), 101.6 (OCH_2O), 61.4 ($COO\mathbf{CH_2}CH_3$), 24.3 (CH_3 pyridine), 13.7 ($COOCH_2\mathbf{CH_3}$) ppm.

Ethyl 4-amino-3-cyano-10-(3,4-dimethoxyphenyl)-8-methylpyrido-[2,3:3,4]pyrazolo[5,1-c][1,2,4]triazine-9-carboxylate (12b): Yellow crystals; IR (ν_{max}): 3290, 3185 (NH_2), 2225 (CN), 1720 (CO ester) cm^{-1}; ^1H NMR (δ): 1.03 (t, *J* = 6.9 Hz, 3H, $COOCH_2\mathbf{CH_3}$), 2.71 (s, 3H, CH_3 pyridine), 3.76, 3.87 (two s, 6H, two OCH_3), 4.15 (q, *J* = 6.9 Hz, 2H, $COO\mathbf{CH_2}CH_3$), 7.12-7.25 (m, 3H, ArH's), 9.45 (s, br., 2H, NH_2) ppm.

Ethyl 4-amino-10-(1,3-benzodioxol-5-yl)-3-aminocarbonyl-8-methyl- pyrido[2,3:3,4]pyrazolo[5,1-c][1,2,4]triazine-9-carboxylate (13a): Yellow crystals; IR (ν_{max}): 3480, 3441, 3289, 3142 (two NH_2), 1710 (CO ester), 1671 (CO amide) cm^{-1}; ^1H NMR (δ): 0.98 (t, *J* = 6.9 Hz, 3H, $COOCH_2\mathbf{CH_3}$), 2.66 (s, 3H, CH_3 pyridine), 4.13 (q, *J* = 6.9 Hz, 2H, $COO\mathbf{CH_2}CH_3$), 6.11 (s, 2H, OCH_2O), 6.85-7.18 (m, 3H, ArH's), 9.49, 9.83, 10.20, 10.65 (4s, 4H, two NH_2) ppm.

Ethyl 4-amino-3-aminocarbonyl-10-(3,4-dimethoxyphenyl)-8-methylpyrido[2,3:3,4]pyrazolo[5,1-c][1,2,4]triazine-9-carboxylate (13b): Yellow crystals; IR (ν_{max}): 3475, 3438, 3280, 3140 (two NH_2), 1708 (CO ester), 1667 (CO amide) cm^{-1}; ^1H NMR (δ): 0.96 (t, *J* = 6.9 Hz, 3H, $COOCH_2\mathbf{CH_3}$), 2.65 (s, 3H, CH_3 pyridine), 3.75, 3.86 (two s, 6H, two OCH_3), 4.12 (q, *J* = 6.9 Hz, 2H, $COO\mathbf{CH_2}CH_3$), 6.70-7.15 (m, 3H, ArH's), 9.45, 9.80, 10.06, 10.57 (4s, 4H, two NH_2) ppm.

Ethyl 4-amino-10-(1,3-benzodioxol-5-yl)-9-ethoxycarbonyl-8-methylpyrido[2,3:3,4]pyrazolo[5,1-c][1,2,4]triazine-3-carboxylate (14a): Yellow crystals; IR (ν_{max}): 3395, 3263 (NH_2), 1725, 1697 (two CO ester) cm^{-1}; ^1H NMR (δ): 1.04 (t, *J* = 6.9 Hz, 3H, $COOCH_2\mathbf{CH_3}$ pyridine), 1.36 (t, *J* = 7.2 Hz, 3H, $COOCH_2\mathbf{CH_3}$ triazine), 2.68 (s, 3H, CH_3 pyridine), 4.14 (q, *J* = 6.9 Hz, 2H, $COO\mathbf{CH_2}CH_3$ pyridine), 4.44 (q, *J* = 7.2 Hz, 2H,

COO**CH$_2$**CH$_3$ triazine), 6.14 (s, 2H, OCH$_2$O), 6.99-7.18 (m, 3H, ArH's), 8.74, 9.37 (two s, 2H, NH$_2$); ^{13}C NMR (δ): 168.1, 165.3 (two **COO**CH$_2$CH$_3$), 160.8-102.1 (14 aromatic C's), 101.5 (OCH$_2$O), 61.5, 61.4 (two COO**CH$_2$**CH$_3$), 24.3 (CH$_3$ pyridine), 14.2 and 13.7 (two COOCH$_2$**CH$_3$**) ppm.

Ethyl 4-amino-10-(3,4-dimethoxyphenyl)-9-ethoxycarbonyl-8-methylpyrido[2,3:3,4]pyrazolo[5,1-c][1,2,4]triazine-3-carboxylate (14b): Yellow crystals; IR (ν$_{max}$): 3395, 3269 (NH$_2$), 1718, 1693 (two CO ester) cm^{-1}; ^{1}H NMR (δ): 1.05 (t, *J* = 6.9 Hz, 3H, COOCH$_2$**CH$_3$** pyridine), 1.38 (t, *J* = 7.2 Hz, 3H, COOCH$_2$**CH$_3$** triazine), 2.70 (s, 3H, CH$_3$ pyridine), 3.77, 3.87 (two s, 6H, two OCH$_3$), 4.16 (q, *J* = 6.9 Hz, 2H, COO**CH$_2$**CH$_3$ pyridine), 4.48 (q, *J* = 7.2 Hz, 2H, COO**CH$_2$**CH$_3$ triazine), 7.10 - 7.26 (m, 3H, ArH's), 8.9 (s, br., 2H, NH2) ppm.

Ethyl 3-acetyl-10-(1,3-benzodioxol-5-yl)-4,8-dimethylpyrido-[2,3:3,4]pyrazolo[5,1-c][1,2,4]triazine-9-carboxylate (15a): Yellow crystals; IR (ν$_{max}$): 1720 (CO ester), 1687 (CO acetyl) cm^{-1}.

Ethyl 3-acetyl-10-(3,4-dimethoxyphenyl)-4,8-dimethylpyrido-[2,3:3,4]pyrazolo[5,1-c][1,2,4]triazine-9-carboxylate (15b): Yellow crystals; IR (ν$_{max}$): 1723 (CO ester), 1692 (CO acetyl) cm^{-1}; ^{1}H NMR (δ): 1.07 (t, *J* = 6.9 Hz, 3H, COOCH$_2$**CH$_3$**), 2.75 (s, 3H, CH$_3$ pyridine), 2.87 (s, 3H, CH$_3$ triazine), 3.20 (s, 3H, CH$_3$ acetyl), 3.77, 3.90 (two s, 6H, two OCH$_3$), 4.17 (q, *J* = 6.9 Hz, 2H, COO**CH$_2$**CH$_3$), 7.18-7.28 (m, 3H, ArH's) ppm.

Ethyl 10-(1,3-benzodioxol-5-yl)-9-ethoxycarbonyl-4,8-dimethyl-pyrido[2,3:3,4]pyrazolo[5,1-c][1,2,4]triazine-3-carboxylate (16a): Yellow crystals; IR (ν$_{max}$): 1718, 1700 (two CO ester) cm^{-1}; ^{1}H NMR (δ): 0.95 (t, *J* = 6.9 Hz, 3H, COOCH$_2$**CH$_3$** pyridine), 1.10 (t, *J* = 7.2 Hz, 3H, COOCH$_2$CH$_3$ triazine), 2.70 (s, 3H, CH$_3$ pyridine), 2.83 (s, 3H, CH$_3$ triazine), 4.08 (q, *J* = 6.9 Hz, 2H, COO**CH$_2$**CH$_3$ pyridine), 4.24 (q, *J* = 7.2 Hz, 2H, COO**CH$_2$**CH$_3$ triazine), 6.18 (s, 2H, OCH$_2$O), 6.51-7.26 (m, 3H, ArH's) ppm; ^{13}C NMR (δ): 167.6, 167.1 (two **COO**CH$_2$CH$_3$), 162.2-108.2 (14 aromatic C's), 101.2 (OCH$_2$O), 61.8, 61.3 (two COO**CH$_2$**CH$_3$), 24.4, 23.4 (two CH$_3$), 13.8, 13.6 (two COOCH$_2$**CH$_3$**) ppm.

Ethyl 10-(3,4-dimethoxyphenyl)-9-ethoxycarbonyl-4,8-dimethyl pyrido[2,3:3,4]pyrazolo[5,1-c][1,2,4]triazine-3-carboxylate (16b): Yellow crystals; IR (ν$_{max}$): 1740, 1718 (two CO ester) cm^{-1}; ^{1}H NMR (δ): 1.07 (t, *J* = 6.9 Hz, 3H, COOCH$_2$**CH$_3$** pyridine), 1.41 (t, *J* = 7.2 Hz, 3H, COOCH$_2$**CH$_3$** triazine), 2.74 (s, 3H, CH$_3$ pyridine), 3.18 (s, 3H, CH$_3$ triazine), 3.78, 3.89 (two s, 6H, two OCH$_3$), 4.20 (q, *J* = 6.9 Hz, 2H, COO**CH$_2$**CH$_3$ pyridine), 4.52 (q, *J* = 7.2 Hz, 2H, COO**CH$_2$**CH$_3$ triazine), 7.13-7.31 (m, 3H, ArH's) ppm.

Ethyl 10-(1,3-benzodioxol-5-yl)-9-ethoxycarbonyl-8-methyl-4-phenylpyrido[2,3:3,4]pyrazolo[5,1-c][1,2,4]triazine-3-carboxylate (17a): Yellow crystals; IR (ν$_{max}$): 1722, 1710 (two CO ester) cm^{-1}.

Ethyl 10-(3,4-dimethoxyphenyl)-9-ethoxycarbonyl-8-methyl-4-phenylpyrido[2,3:3,4]pyrazolo[5,1-c][1,2,4]triazine-3-carboxylate (17b): Yellow crystals; IR (ν_{max}): 1727, 1712 (two CO ester) cm^{-1}; ^1H NMR (δ): 1.08 (m, 6H, two $COOCH_2\mathbf{CH_3}$), 2.73 (s, 3H, CH_3 pyridine), 3.79, 3.90 (two s, 6H, two OCH_3), 4.25 (m, 4H, two $COO\mathbf{CH_2}CH_3$), 7.16-7.80 (m, 8H, ArH's) ppm.

Ethyl 3-acetyl-10-(1,3-benzodioxol-5-yl)-8-methyl-4-phenylpyrido-[2,3:3,4]Pyrazolo[5,1-c][1,2,4]triazine-9-carboxylate (18a): Yellow crystals; IR (ν_{max}): 1716 (CO ester), 1676 (CO acetyl) cm^{-1}; ^1H NMR (δ): 1.10 (t, J = 6.9 Hz, 3H, $COOCH_2\mathbf{CH_3}$), 2.78 (s, 3H, CH_3 pyridine), 3.03 (s, 3H, $COCH_3$), 4.21 (q, J = 6.9 Hz, 2H, $COO\mathbf{CH_2}CH_3$), 6.13 (s, 2H, OCH_2O), 7.09-7.94 (m, 8H, ArH's) ppm.

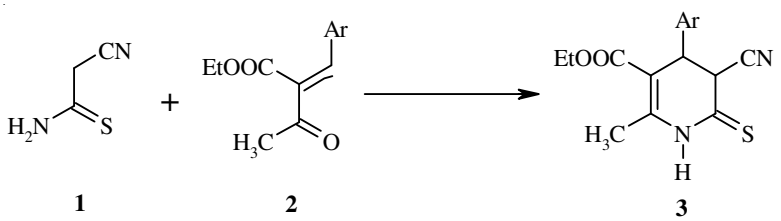
Ethyl 3-acetyl-10-(3,4-dimethoxyphenyl)-8-methyl-4-phenylpyrido-[2,3:3,4]pyrazolo[5,1-c][1,2,4]triazine-9-carboxylate (18b): Yellow crystals; IR (ν_{max}): 1714 (CO ester) and 1670 (CO acetyl) cm^{-1}; ^1H NMR (δ): 1.07 (t, J = 6.9 Hz, 3H, $COOCH_2\mathbf{CH_3}$), 2.77 (s, 3H, CH_3 pyridine), 3.03 (s, 3H, $CO\mathbf{CH_3}$), 3.75, 3.87 (two s, 6H, two OCH_3), 4.21 (q, J = 6.9 Hz, 2H, $COO\mathbf{CH_2}CH_3$), 7.13-7.94 (m, 8H, ArH's) ppm.

Ethyl 10-(1,3-benzodioxol-5-yl)-3-benzoyl-8-methyl-4-phenyl-pyrido-[2,3:3,4]pyrazolo[5,1-c][1,2,4]triazine-9-carboxylate (19a): Yellow crystals; IR (ν_{max}): 1715 (CO ester), 1663 (CO benzoyl) cm^{-1}; ^1H NMR (δ): 1.10 (t, J = 6.9 H z, 3H, $COOCH_2\mathbf{CH_3}$), 2.75 (s, 3H, CH_3 pyridine), 4.22 (q, J = 6.9 Hz, 2H, $COO\mathbf{CH_2}CH_3$), 6.14 (s, 2H, OCH_2O), 7.12-7.92 (m, 13H, ArH's) ppm.

Ethyl 3-benzoyl-10-(3,4-dimethoxyphenyl)-8-methyl-4-phenyl-pyrido-[2,3:3,4]pyrazolo[5,1-c][1,2,4]triazine-9-carboxylate (19b): Yellow crystals; IR (ν_{max}): 1704 (CO ester), 1665 (CO benzoyl) cm^{-1}; ^1H NMR (δ): 1.08 (t, J = 6.9 Hz, 3H, $COOCH_2\mathbf{CH_3}$), 2.75 (s, 3H, CH_3 pyridine), 3.78, 3.88 (two s, 6H, two OCH_3), 4.21 (q, J = 6.9 Hz, 2H, $COO\mathbf{CH_2}CH_3$), 7.16-7.92 (m, 13H, ArH's) ppm.

RESULTS AND DISCUSSION

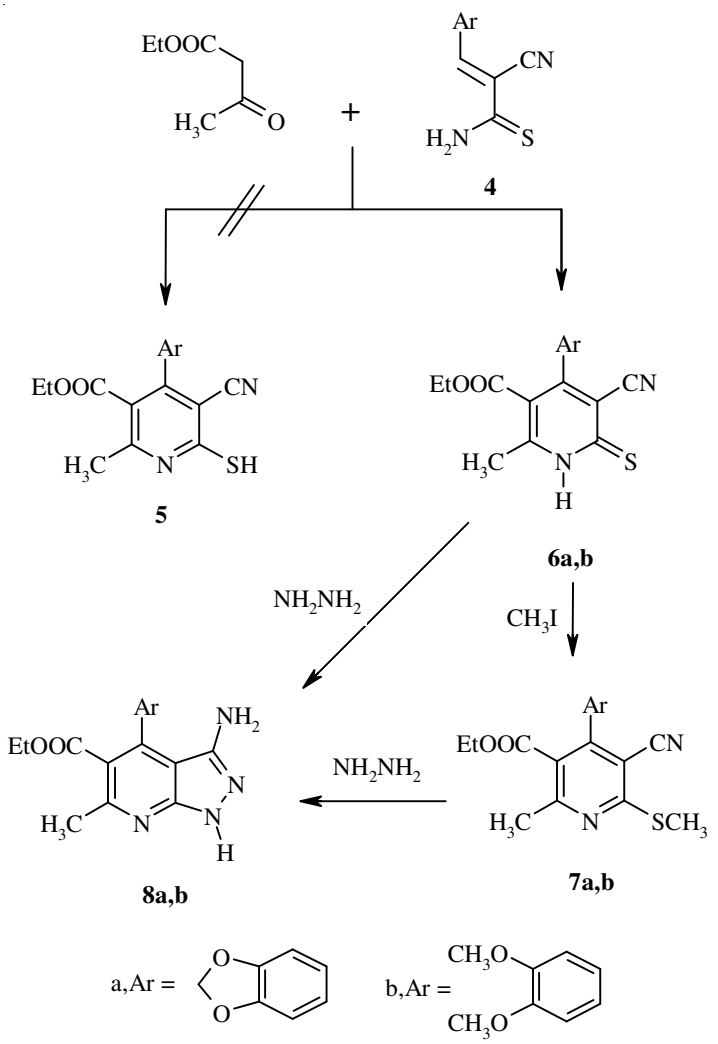
It was reported[14] that arylidene acetoacetic ester **2** reacted with cyanothioacetamide **1** to give tetrahydrothioxopyridine (**3**) (**Scheme-I**).



1 **2** **3**

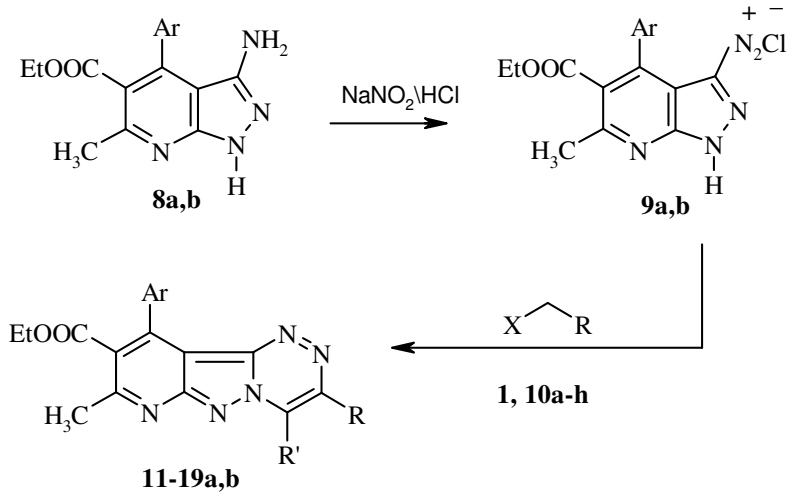
Scheme-I

But recently, it has been found that, the arylidene cyanothioacetamide (**4**) reacts with ethyl acetoacetate to afford the corresponding pyridine thiol derivatives (**5**)[2] and dihydrothioxopyridine derivatives (**6**)[6], In present work, treatment of **4a,b** with ethyl acetoacetate in dioxane in the presence of piperidine afforded dihydrothioxopyridine derivatives (**6a,b**)[5], neither tetrahydrothioxopyridine (**3**), nor pyridine thiol (**5**) were detected (**Scheme-II**). The structures of **6a,b** were inferred on the basis of their elemental analyses and spectral data. Thus, each of the products isolated exhibits NH, CN and C=O (ester) absorptions near 3450, 2220 and 1707 cm^{-1}, respectively. Furthermore, ^1H NMR spectra of **6a,b** showed a common broad signal near (δ) 13.9 ppm, assignable to the NH proton resonance.



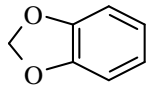
Scheme-II

Compounds **6a,b** were reacted with methyl iodide in sodium methoxide solution to give 2-methylthiopyridine derivatives (**7a,b**). The structures of **7a,b** were confirmed from their elemental analyses and spectral data. Treatment of **7a,b** and **6a,b** with excess amount of hydrazine hydrate in ethanol gave products free of sulfur, which formulated as aminopyrazolopyridine derivatives (**8a,b**) (**Scheme-II**). The structures of **8a,b** were assigned from their elemental analyses and spectral data. The IR spectra of **8a,b**, in each case, show NH, NH_2 and C=O (ester) absorptions 3445, 3290, 3190 and 1715 cm^{-1}, respectively. ^1H NMR spectra reveal signals of NH and NH_2 protons resonance near (δ) 12.1 and 4.3 ppm, in addition to the usual proton signals. ^{13}C NMR and the mass spectra of **8a,b** are compatible with the proposed structures.

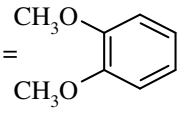


R \ X \ R'		
1	11	$CSNH_2$ \ CN \ NH_2
10a	12	CN \ CN \ NH_2
10b	13	$CONH_2$ \ CN \ NH_2
10c	14	$COOC_2H_5$ \ CN \ NH_2
10d	15	$COCH_3$ \ $COCH_3$ \ CH_3
10e	16	$COOC_2H_5$ \ $COCH_3$ \ CH_3
10f	17	$COOC_2H_5$ \ COPh \ Ph
10g	18	$COCH_3$ \ COPh \ Ph
10h	19	COPh \ COPh \ Ph

a,Ar =



b,Ar =



Scheme-III

Next, the diazonium salts of **8a,b** were coupled with several active methylene compounds **1** and **10a-h** in ethanol, The products were formulated as pyridopyrazolotriazine derivatives **11-19a,b**, respectively. The structures of **11-19a,b** were inferred on the basis of elemental analyses and spectral data. The IR spectra, in each case, reveal the absence of NH and NH_2 absorption bands and appearance of new bands due to introduction of new groups. ^{1}H NMR spectra, also, show the absence of NH and NH_2 proton signals. Furthermore, both ^{13}C NMR and mass spectra of **11-19a,b** were consistent with their structures (**Scheme-III**).

TABLE-1
PHYSICAL PROPERTIES AND ELEMENTAL ANALYSES OF SYNTHESIZED COMPOUNDS

Compd. no.	m.p. (ºC)	Yield (%)	m.f. / m.w.	Calcd. (Found) %		
				C	H	N
6a	245-7[a]	61	$C_{17}H_{14}N_2O_4S$ 342.29	59.64 (59.70)	4.12 (4.15)	8.18 (8.14)
6b	226-8[a]	65	$C_{18}H_{18}N_2O_4S$ 358.33	60.33 (60.22)	5.06 (4.94)	7.81 (7.79)
7a	113-5[a]	74	$C_{18}H_{16}N_2O_4S$ 356.32	60.69 (60.57)	4.52 (4.50)	7.86 (8.12)
7b	127-9[a]	77	$C_{19}H_{20}N_2O_4S$ 372.36	61.28 (61.31)	5.41 (5.36)	7.52 (7.61)
8a	261-3[a]	81	$C_{17}H_{16}N_4O_4$ 340.32	59.99 (60.13)	4.73 (4.72)	16.46 (16.52)
8b	238-40[a]	83	$C_{18}H_{20}N_4O_4$ 356.36	60.66 (60.64)	5.65 (5.58)	15.72 (15.64)
11a	>300[b]	77	$C_{20}H_{17}N_7O_4S$ 451.38	53.21 (53.17)	3.79 (3.77)	21.72 (21.68)
11b	>300[a]	72	$C_{21}H_{21}N_7O_4S$ 467.42	53.95 (53.87)	4.52 (4.38)	20.97 (20.88)
12a	267-9[c]	67	$C_{20}H_{15}N_7O_4$ 417.36	57.55 (57.36)	3.62 (3.63)	23.49 (23.23)
12b	240-2[a]	70	$C_{21}H_{19}N_7O_4$ 433.41	58.19 (58.20)	4.41 (4.42)	22.62 (22.47)
13a	>300[b]	71	$C_{20}H_{17}N_7O_5$ 435.38	55.16 (55.21)	3.93 (4.11)	22.52 (22.61)
13b	>300[b]	76	$C_{21}H_{21}N_7O_5$ 451.42	55.86 (55.90)	4.68 (4.72)	21.71 (21.87)

Compd. no.	m.p. (ºC)	Yield (%)	m.f. / m.w.	Calcd. (Found) %		
				C	H	N
14a	258-60[b]	69	$C_{22}H_{20}N_6O_6$ 464.42	56.89 (56.79)	4.34 (4.41)	18.09 (18.02)
14b	271-3[b]	73	$C_{23}H_{24}N_6O_6$ 480.46	57.49 (57.40)	5.03 (4.78)	17.49 (17.38)
15a	270-2[a]	81	$C_{22}H_{19}N_5O_5$ 433.40	60.96 (60.88)	4.41 (4.26)	16.15 (16.06)
15b	195-7[a]	83	$C_{23}H_{23}N_5O_5$ 449.44	61.45 (61.60)	5.15 (5.22)	15.58 (15.65)
16a	250-2[b]	74	$C_{23}H_{21}N_5O_6$ 463.43	59.60 (59.58)	4.56 (4.48)	15.11 (15.02)
16b	191-2[a]	78	$C_{24}H_{25}N_5O_6$ 479.47	60.11 (60.08)	5.25 (5.16)	14.60 (14.48)
17a	230-2[a]	72	$C_{28}H_{23}N_5O_6$ 525.49	63.99 (63.92)	4.41 (4.36)	13.32 (13.26)
17b	203-5[a]	75	$C_{29}H_{27}N_5O_6$ 541.54	64.31 (64.28)	5.02 (4.91)	12.93 (12.76)
18a	181-3[a]	90	$C_{27}H_{21}N_5O_5$ 495.47	65.44 (65.61)	4.27 (4.31)	14.13 (14.32)
18b	171-3[a]	88	$C_{28}H_{25}N_5O_5$ 511.51	65.74 (65.81)	4.92 (4.94)	13.69 (13.71)
19a	271-3[a]	81	$C_{32}H_{23}N_5O_5$ 557.53	68.93 (68.81)	4.15 (4.10)	12.56 (12.37)
19b	266-8[b]	71	$C_{32}H_{27}N_5O_5$ 573.58	69.09 (68.92)	4.74 (4.68)	12.21 (12.14)

Crystallized from= [a] ethanol [b] ethanol-acetic acid [c] tetrahydrofuran

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