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SYNTHESIS OF CONDENSED PYRIDO [1, 2-a] PYRIMIDINE AND PYRIMIDO [4, 5-d] PYRIMIDINE DERIVATIVES FROM CYANOKETENE DITHIOACETAL

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ABSTRACT

Cyanoketene dithioacetal are known to undergo cyclocondensation with 2-amino pyridyl amines to give pyrimidine derivatives. The aim of the present investigation has been to examine the versatility of cyanoketene dithioacetal in the synthesis of substituted pyrido [1,2-a] pyrimidine and pyrimido [4,5-d] pyrimidine derivatives from 2-aminopyridines. Cyanoketene dithioacetal **(1)** on reaction with variously substituted 2 -aminopyridine derivatives **(2a-f)** formed 2-ethoxy-3-cyano-4-oxo-4 –*H*-pyrido [1,2-a] pyrimidine **(3a-f)** and 2-ethoxy-(2-methylthio)-3-cyano-4-oxo-4 –*H*-pyrido [1,2-a] pyrimidine derivatives **(4a-f)** in high yields. Subsequent reactions of **(4)** with (i) primary amines (ii) hydrazine hydrate (iii) hydroxyl amine (iv) acetamidine hydrochloride afforded the corresponding pyrimidine derivatives **(5-6a-f)**, pyrazole derivatives **(7a-f)**, isoxazole derivatives **(8a-f)** and pyrimido [4,5-d] pyrimidine derivatives **(9a-f),** respectively in good yields.

Key words : Synthesis, Pyrido-pyrimidine, Cyanoketene dithioacetal.

INTRODUCTION

The importance of pyrido[1,2-a] pyrimidines and pyrimido[4,5-d] pyrimidines are well recognized by synthetic as well as biological chemists[1] and therefore, their accessibility through easily available precursors is important in the development of chemistry of these materials.

Heterocyclic ketene N,S-acetals[2-5], aminals[6-12] as well as ketoketene and cyanoketene S,S-acetals[13-16] are important synthons for the synthesis of a wide variety of fused heterocycles . It has been reported[17] that these synthons act as very powerful 1,3-dipolarophiles to afford a very convenient synthetic entry to a variety of condensed and fused heterocycles. This prompted us to employ these reagents in the synthesis of

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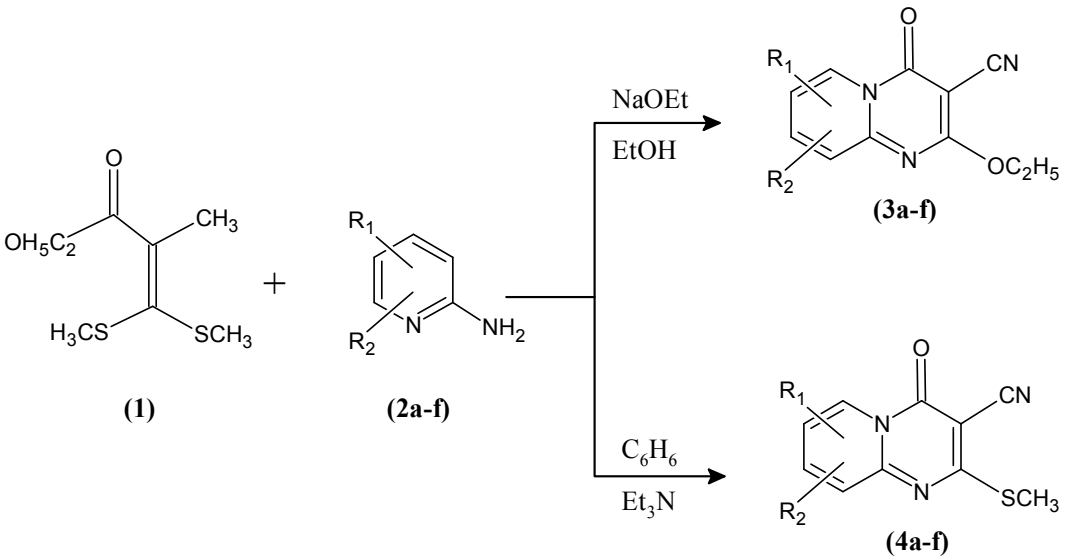
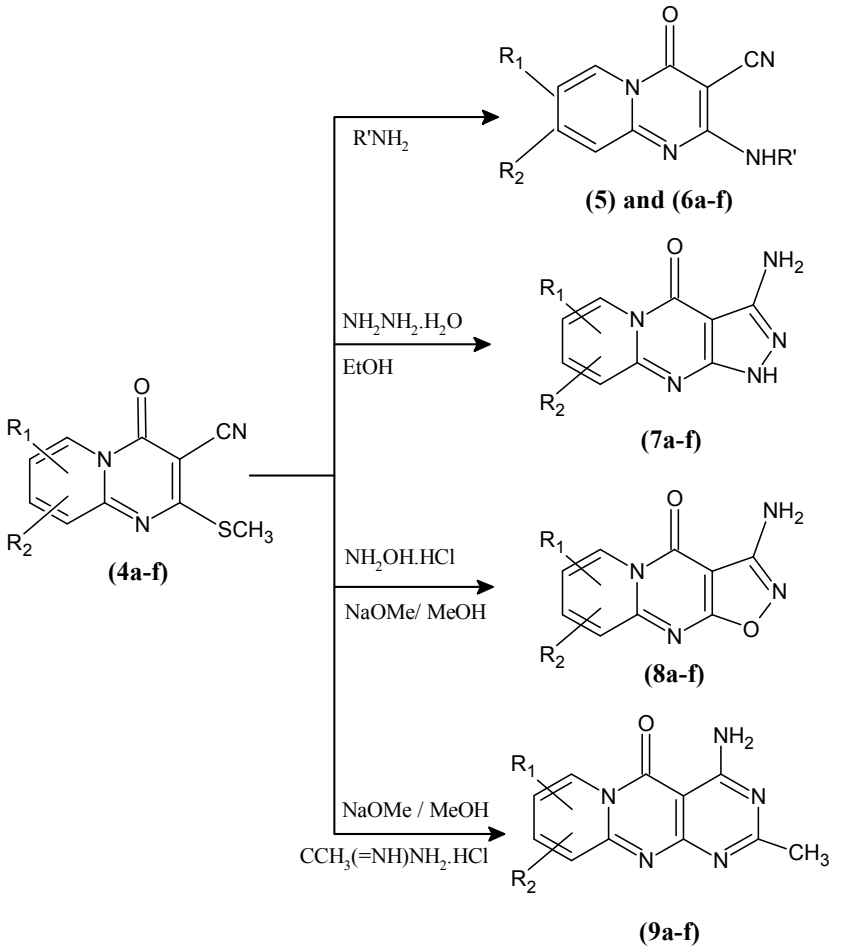
pyrido[1,2-a] pyrimidine **(3~8a-f)** and pyrimido[4,5-d] pyrimidine **(9a-f)** derivatives from cyanoketene diothioacetal **(1)** through **Schemes I and II**.



Scheme I

	3-4
a	**R_1 = H, R_2 = CH_3**
b	**R_1 = H, R_2 = CH_3**
c	**R_1 = H, R_2 = CH_3**
d	**R_1 = H, R_2 = Cl**
e	**R_1 = Br, R_2 = Br**
f	**R_1 = H, R_2 = NO_2**



Scheme 2

	5	6	7-9
a	$R_1 = H, R_2 = CH_3, R' = CH_3$	$R_1 = H, R_2 = CH_3, R' = C_2H_5$	$R_1 = H, R_2 = CH_3$
b	$R_1 = H, R_2 = CH_3, R' = CH_3$	$R_1 = H, R_2 = CH_3, R' = C_2H_5$	$R_1 = H, R_2 = CH_3$
c	$R_1 = H, R_2 = CH_3, R' = CH_3$	$R_1 = H, R_2 = CH_3, R' = C_2H_5$	$R_1 = H, R_2 = CH_3$
d	$R_1 = H, R_2 = Cl, R' = CH_3$	$R_1 = H, R_2 = Cl, R' = C_2H_5$	$R_1 = H, R_2 = Cl$
e	$R_1 = Br, R_2 = Br, R' = CH_3$	$R_1 = Br, R_2 = Br, R' = C_2H_5$	$R_1 = Br, R_2 = Br$
f	$R_1 = H, R_2 = NO_2, R' = CH_3$	$R_1 = H, R_2 = NO_2, R' = C_2H_5$	$R_1 = H, R_2 = NO_2$

EXPERIMENTAL

General method for the preparation of 2-ethoxy-3-cyano-4-oxo-4H-pyrido [1,2-a] pyrimidine (3a-f)

2-Aminopyridine **(2a)** (1 mmol), sodium ethoxide (1 mmol) and cyanoketene dithioacetal **(1)** (1 mmol) were taken in 30 mL ethanol and refluxed for 3 hr. The solvent was removed in *vauco* and the residue was washed with diethyl ether (2 x 5 mL) and purified by recrystallization from methanol and dried to give **(3a)**, yield 71 %, m. p. 257°C. Other compounds **(3 b-f)** were similarly prepared from **(2 b-f)**.

(3a) 2-Ethoxy-9-methyl-4-oxo-4H-pyrido [1,2-a] pyrimidine-3-carbonitrile : yield 67%, m. p. 245°C ; Calc : C, 62.87; H, 4.84; N, 18.33; O, 13.96; Found : C, 62.45; H, 4.66; N, 18.52.; O, 13.84.; ν_{max} 2220 (CN),1650 (CO) cm^{-1}; NMR(DMSO-d_6) 7.28 (1H, d, = CH), 6.3 (1H, d, = CH), 5.77(1H, q, = CH), 4.0 (2H, q, CH_2), 1.71 (3H, s, CH_3), 1.22 (3H, t, CH_3); MS (EI, 70 eV) : *m/z* 230.09 (13.2%).

(3b) 2-Ethoxy-8-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carbonitrile; yield 69%, m.p. 245° C ; calc : C, 62.87; H, 4.84; N, 18.33; O, 13.96; Found : C, 62.49; H, 4.68; N, 18.56.; O, 13.89.; ν_{max} 2215 (CN), 1643(CO) cm^{-1}; NMR(DMSO-d_6) 7.28 (1H, d, = CH), 5.77 (1H, d,= CH), 5.0(1H, s, = CH), 4.0 (2H, q, CH_2), 1.71 (3H, s, CH_3), 1.22 (3H, t, CH_3); MS (EI, 70 eV) : *m/z* 230 (13.2%).

(3c) 2-Ethoxy-7-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carbonitrile; yield 65%, m.p. 245°C; Calc : C, 62.87; H, 4.84; N, 18.33; O, 13.96; Found : C, 62.48; H, 4.62; N, 18.54.; O, 13.86.; ν_{max} 2214 (CN), 1648(CO) cm^{-1}; NMR(DMSO-d_6) 7.06 (1H, s, = CH), 6.5 (1H, d,= CH), 5.2 (1H, d, = CH), 4.0 (2H, q, CH_2), 1.71 (3H, s, CH_3),1.22 (3H, t, CH_3),; MS (EI, 70 eV) : *m/z* 230 (13.2%).

(3d) 2-Ethoxy-7-chloro-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carbonitrile; yield 73%, m. p. 235° C; Calc : C, 52.92; H, 3.23; Cl, 14.20; N, 16.83; O, 12.82 : Found C, 52.85; H, 3.41; Cl, 14.36; N, 16.71; O, 12.59; ν_{max} 2210(CN), 1630 (CO), 771(C-Cl) cm^{-1}; NMR(DMSO-d_6) 7.46 (1H, s, = CH), 6.5 (1H, d,= CH), 5.2 (1H, d, = CH), 4.0 (2H, q, CH_2), 1.22 (3H, t, CH_3); MS (EI, 70 eV) : *m/z* 250.03 (13.1%).

(3e) 2 – Ethoxy – 7, 9 – dibromo – 4 – oxo – 4 H – pyrido[1,2-a] pyrimidine – 3 – carbonitrile; yield 66%, m.p. 198°C; Calc : C, 35.42; H, 1.89; Br, 42.84; N, 11.27; O, 8.58; Found : C, 35.56; H, 1.96; Br, 42.66; N, 11.38; O, 8.70; ν_{max} 2205 (CN), 1634(CO),

781(C-Br) cm^{-1}; NMR(DMSO-d_6) 7.73 (1H, s, = CH), 6.9 (1H, s,= CH), 4.0 (2H, q, CH_2), 1.22 (3H, t, CH_3); MS (EI, 70 eV) : *m/z* 373.89 (13.1%).

(3f) 2-Ethoxy-7-nitro-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carbonitrile; yield 74%, m. p. 189°C; Calc : C, 50.77; H, 3.10; N, 21.53; O, 24.60; Found : C, 50.62; H, 3.33; N, 21.46; O, 24.76; ν_{max} 2210 (CN), 1648 (CO), 1510(NO_2) cm^{-1}; NMR(DMSO-d_6) 8.58 (1H, s, = CH), 6.5 (1H, d,= CH), 5.2 (1H, d, = CH), 4.0 (2H, q, CH_2), 1.22 (3H, t, CH_3); MS (EI, 70 eV) : *m/z* 261.06 (12.1%).

General method for the preparation of 2-methylthio-3-cyano-4-oxo-4H- pyrido [1, 2-a] pyrimidine (4a-f)

2-Aminopyridine **(2a)** (1 mmol) and cyanoketene dithioacetal **(1)** (1 mmol) were taken in 30 mL benzene and 5 mL triethylamine was added to it. The mixture was refluxed for 3 hr. The solvent was removed in *vauco* and the residue was washed with diethyl ether (2 x 5 mL) and purified by recrystallization from ethyl acetate to afford **(4a),** yield 70 %, m.p. 209-210°C. Other compounds **(4 b-f)** were similarly prepared from **(2 b-f)**.

(4a) : 9-Methyl-2-(methylthio)-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carbonitrile; yield 64%, m.p.209-210°C; Calc : C, 57.13; H, 3.92; N, 18.17; O, 6.92; S, 13.86; Found : C, 57.37; H, 3.78; N, 18.31; O, 6.77; S, 13.98; ν_{max} 2206(C≡N), 1697 (CO), 1540(C= N) cm^{-1}; NMR(DMSO-d_6) 7.28 (1H, d, = CH), 6.3 (1H, d, = CH), 5.77 (1H, q,= CH), 2.25 (3H, s, CH_3), 1.71(3H, s, CH_3); MS (EI, 70 eV) : *m/z* 232 (13.8%).

(4b) 8-Methyl-2-(methylthio)-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carbonitrile; yield 68%, m.p. 209-210°C; Calc : C, 57.13; H, 3.92; N, 18.17; O, 6.92; S, 13.86; Found : C, 57.39; H, 3.78; N, 18.32; O, 6.79; S, 13.94; ν_{max} 2214(C≡N), 1689 (CO), 1550(C= N) cm^{-1}; NMR(DMSO-d_6) 7.28 (1H, d, = CH), 5.77 (1H, d, = CH), 5.0 (1H, s, = CH), 2.25 (3H, s, CH_3), 1.71 (3H, s, CH_3); MS (EI, 70 eV) : *m/z* 232 (13.8%).

(4c) 7-Methyl-2-(methylthio)-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carbonitrile; yield 70%, m.p. 209-210°C; Calc : C, 57.13; H, 3.92; N, 18.17; O, 6.92; S, 13.86; Found : C, 57.40; H, 3.77; N, 18.35; O, 6.80; S, 13.91; ν_{max} 2215(C≡N), 1699 (CO), 1560(C= N) cm^{-1}; NMR(DMSO-d_6) 7.06 (1H, s, = CH), 6.5(1H, d, = CH), 5.2 (1H, d, = CH), 2.25 (3H, s, CH_3), 1.71 (3H, s, CH_3); MS (EI, 70 eV) : *m/z* 232 (13.8%).

(4d) 7-Chloro-2-(methylthio)-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carbonitrile ; yield 72%. m.p. 257°C; Calc : C, 47.72; H, 2.40; Cl, 14.09; N, 16.70; O, 6.36; S, 12.74;

Found : C, 47.34; H, 2.68; Cl, 14.48; N, 16.49; O, 6.65; S, 12.98; ν_{max} 2204(C≡N), 1689 (CO), 1590(C= N), 730 (C-Cl) cm^{-1}, NMR(DMSO-d_6) 7.46 (1H, s, = CH), 6.5 (1H, d, = CH), 5.2 (1H, d, = CH), 2.25 (3H, s, CH_3); MS (EI, 70 eV) : *m/z* 252.00 (10.9%).

(4e) 7, 8 – Dibromo – 2 - (methylthio) – 4 – oxo - 4H - pyrido[1,2-a] pyrimidine -3 - carbonitrile; yield 65%, m.p. 171°C; Calc : C, 32.03; H, 1.34; Br, 42.61; N, 11.20; O, 4.27; S, 8.55 ; Found : C, 32.52; H, 1.49; Br, 42.28; N, 11.78; O, 4.11; S, 8.78 ; ν_{max} 2206 (C≡N), 1697 (CO), 1590 (C= N), 771 (C-Br) cm^{-1}, NMR (DMSO-d_6) 7.73 (1H, s, = CH), 6.9 (1H, s, = CH), 2.25 (3H, s, CH_3); MS(EI, 70 eV) : *m/z* 375.85 (12.7%).

(4f) 2-(Methylthio)-7-nitro-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carbonitrile; yield 74 %, m.p. 166°C; Calc : C, 45.80; H, 2.31; N, 21.36; O, 18.30; S, 12.23 ; Found : C, 45.47; H, 2.76; N, 21.13; O, 18.67; S, 12.73; ν_{max} 2202(C≡N), 1635 (CO), 1573(C= N), 1506(NO_2) cm^{-1} ; NMR (DMSO-d_6) 8.58 (1H, s, = CH), 6.5 (1H, d, = CH), 5.2 (1H, d, = CH), 2.25(3H, s, CH_3); MS(EI, 70 eV) : *m/z* 263.02 (11.8%).

General method for the preparation of 2-amino-3-cyano-4-oxo-4H-pyrido[1,2-a]pyrimidine (5a~f) and (6a~f)

2-Methylthio-3-cyano-4-oxo-4H- pyrido[1,2-a]pyrimidine **(5a)** (1 mmol) and methyl amine (2 mmol) were dissolved in 30 mL of ethanol and refluxed for 6 hr (monitored by TLC). After evaporation of the solvent, residue was purified by a silica-gel column using ethyl acetate-hexane (1 : 1) mixture gives **(5a)**. yield 67 %, m.p. 200°C. Other compounds **(5 b-f)** and **(6 a-f)** were similarly prepared from 4 a~f and respective amines.

(5a) 9 – Methyl – 2 - (methylamino) – 4 – oxo - 4H – pyrido [1, 2-a] pyrimidine – 3 - carbonitrile; yield 67%, m.p. 200°C; Calc : C, 61.67; H, 4.71; N, 26.15; O, 7.47 ;Found : C, 61.24; H, 4.32; N, 26.49; O, 7.12 ; ν_{max} 3450(NH), 2210 (C≡N), 1697 (CO) cm^{-1}, NMR (DMSO-d_6) 7.18 (1H, d, = CH), 6.3 (1H, d, = CH), 5.77 (1H, q, = CH), 2.47 (3H, s, CH_3), 2.0 (1H, s, NH), 1.71(3H,s, CH_3). MS(EI, 70 eV) : *m/z* 215.09 (12.1%) :

(5b) 8-Methyl-2-(methylamino)-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carbonitrile : yield 69%, m.p. 200°C; Calc : C, 61.67; H, 4.71; N, 26.15; O, 7.47 ; Found : C, 61.29; H, 4.30; N, 26.52; O, 7.08 ; ν_{max} 3460(NH), 2214(C≡N), 1682(CO) cm^{-1} ; NMR (DMSO-d_6) 7.28(1H, d, = CH), 5.77 (1H, d, = CH), 5.0(1H, s, = CH), 2.47 (3H, s, CH_3), 2.0 (1H, s, NH), 1.71(3H,s, CH_3); MS(EI, 70 eV) : *m/z* 215.09 (12.1%).

(5c) 7-Methyl-2-(methylamino)-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carbonitrile : yield 73%, m.p. 200°C; Calc : C, 61.67; H, 4.71; N, 26.15; O, 7.47 ;Found : C, 61.30; H, 4.28; N, 26.43; O, 7.16 ; ν_{max} 3455(NH), 2213(C≡N), 1690(CO) cm^{-1}; NMR (DMSO-d_6) 7.06 (1H, s, = CH), 6.5 (1H, d, = CH), 5.2 (1H, d, = CH), 2.47 (3H, s, CH_3), 2.0 (1H, s, NH), 1.71 (3H,s, CH_3); MS(EI, 70 eV) : *m/z* 215.09 (12.1%).

(5d) 7-Chloro-2-(methylamino)-4-oxo-4H-pyrido [1,2-a] pyrimidine-3-carbonitrile : yield 72% m.p. 187°C; Calc : C, 51.19; H, 3.01; Cl, 15.11; N, 23.88; O, 6.82 ;Found : C, 51.56; H, 3.43; Cl, 15.67; N, 23.36; O, 6.59 ; IR (KBr) : 3450(NH), 2210(C≡N), 1692(CO) 690(C-Cl) cm^{-1}; NMR (DMSO-d_6) 7.46(1H, s, = CH), 6.5(1H, d, = CH), 5.2(1H, d, = CH), 2.47 (3H, s, CH_3), 2.0 (1H, s, NH); MS(EI, 70 eV) : *m/* 235.03 (12.3%).

(5e) 7, 9 – Dibromo – 2 - (methylamino) – 4 – oxo - 4H – pyrido [1,2-a] pyrimidine – 3 - carbonitrile: yield 66%, m.p. 234°C; Calc : C, 33.55; H, 1.69; Br, 44.64; N, 15.65; O, 4.47; Found : C, 33.96; H, 1.23; Br, 44.76; N, 15.12; O, 4.19 ; IR (KBr) : 3465(NH), 2215(C≡N), 1689(CO), 763(C-Br) cm^{-1}; NMR (DMSO-d_6) 7.73(1H, s, = CH), 6.9 (1H, s, = CH), 2.47 (3H, s, CH_3), 2.0 (1H, s, NH); MS(EI, 70 eV) : *m/z* 358.89 (12.3%).

(5f) 2-(Methylamino)-7-nitro-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carbonitrile : yield 78%, m.p. 187°C; Calc : C, 48.98; H, 2.88; N, 28.56; O, 19.58; Found : C, 48.69; H, 2.56; N, 28.98; O, 19.45 ; IR (KBr) : 3494 (NH), 2200(C≡N), 1643(CO), 1496 (NO_2) cm^{-1}; NMR (DMSO-d_6) 8.58 (1H, s, = CH), 6.5 (1H, d, = CH), 5.2 (1H, d, = CH), 2.47 (3H, s, CH_3), 2.0 (1H, s, NH); MS(EI, 70 eV) : *m/z* 246.06 (11.0%).

(6a) 2 - (Ethylamino) – 9 – methyl – 4 – oxo - 4H – pyrido [1,2-a] pyrimidine – 3 - carbonitrile; yield 65%, m.p. 248°C; Calc : C, 63.15; H, 5.30; N, 24.55; O, 7.01 ; Found : C, 63.35; H, 5.48; N, 24.19; O, 7.34 ; IR (KBr) : 3400 (NH), 2215(C≡N), 1685(CO) cm^{-1} ; NMR (DMSO-d_6) 7.28 (1H, d, = CH), 6.3 (1H, d, = CH), 5.77 (1H, q, = CH), 2.69 (2H, q, CH_2), 2.0 (1H, s, NH), 1.71 (3H, s, CH_3), 1.00 (3H, t, CH_3); MS(EI, 70 eV) : *m/z* 229.10 (14.5%).

(6b) 2-(Ethylamino)-8-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carbonitrile : yield 67%, m.p. 248°C; Calc : C, 63.15; H, 5.30; N, 24.55; O, 7.01 ; Found : C, 63.37; H, 5.51; N, 24.59; O, 7.30 ; IR (KBr) : 3430(NH), 2210(C≡N), 1678(CO) cm^{-1} ; NMR (DMSO-d_6) 7.28(1H, d, = CH), 5.77 (1H, d, = CH), 5.0 (1H, s, = CH), 2.69 (2H, q, CH_2), 2.0 (1H, s, NH), 1.71 (3H, s, CH_3), 1.00 (3H, t, CH_3) ; MS(EI, 70 eV) : *m/z* 229.10 (14.5%).

(6c) 2-(Ethylamino)-7-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carbonitrile : yield 71%, m.p. 248°C; Calc : C, 63.15; H, 5.30; N, 24.55; O, 7.01 ; Found : C, 63.33; H, 5.47; N, 24.60; O, 7.33; IR (KBr) : 3410 (NH), 2214(C≡N), 1678(CO) cm^{-1}; NMR (DMSO-d_6) 7.06(1H, s, = CH), 6.5 (1H, d, = CH), 5.2 (1H, d, = CH) 2.69 (2H, q, CH_2), 2.0 (1H, s, NH), 1.71 (3H, s, CH_3), 1.00 (3H, t, CH_3); MS(EI, 70 eV) : *m/z* 229.10 (14.5%).

(6d) 7-Chloro-2-(ethylamino)-4-oxo-4H-pyrido [1,2-a] pyrimidine-3-carbonitrile : yield 73%, m.p. 176°C; Calc : C, 53.13; H, 3.65; Cl, 14.26; N, 22.53; O, 6.43 ; Found : C, 53.25; H, 3.71; Cl, 14.30; N, 22.24; O, 6.32 ; IR (KBr) : 3440 (NH), 2210(C≡N),1681(CO), 800(C-Cl) cm^{-1}; NMR (DMSO-d_6) 7.46(1H, s, = CH), 6.5(1H, d, = CH), 5.2(1H, d, = CH), 2.69 (2H, q, CH_2), 2.0 (1H, s, NH), 1.00 (3H, t, CH_3); MS(EI, 70 eV) : *m/* 249.05 (12.0%).

(6e) 7, 9 – Dibromo – 2 - (ethylamino) – 4 – oxo - 4H – pyrido [1,2-a] pyrimidine-3 - carbonitrile : yield 64%, m.p. 214°C; Calc : C, 35.51; H, 2.17; Br, 42.96; N, 15.06; O, 4.30 ; Found : C, 35.66; H, 2.34; Br, 42.85; N, 15.27; O, 4.24 ; IR (KBr) : 3420(NH), 2206(C≡N), 1697(CO), 779(C-Br) cm^{-1}; NMR (DMSO-d_6) 7.73(1H, s, = CH), 6.9 (1H, s, = CH), 2.69 (2H, q, CH_2), 2.0 (1H, s, NH), 1.00 (3H, t, CH_3); MS(EI, 70 eV) : *m/z* 372.91 (12.0%).

(6f) 2-(Ethylamino)-7-nitro-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carbonitrile : yield 77%, m.p. 185°C; Calc : C, 50.97; H, 3.50; N, 27.02; O, 18.52 ; Found : C, 50.86; H, 3.38 N, 27.21; O, 18.65 ; IR (KBr) : 3494(NH), 2200(C≡N), 1643(CO), 1496(NO_2) cm^{-1}; NMR (DMSO-d_6) 8.58 (1H, s, = CH), 6.5 (1H, d, = CH), 5.2 (1H, d, = CH), 2.69 (2H, q, CH_2), 2.0 (1H, s, NH), 1.00 (3H, t, CH_3); MS(EI, 70 eV) : *m/z* 260.07 (13.6%).

General method for the preparation of 3-amino–1H-3, 4-dihydropyrazolo [3,4-b] quinolizin-4-one (7a-f)

Hydrazine hydrate (5 mmol) and 2-methylthio-3-cyano-4-oxo-4H- pyrido [1,2-a] pyrimidine **(4a)** were taken in 50 mL of ethanol and refluxed for 3 hr. The solvent was removed and the residue was dissolved in 20 mL of chloroform. On removal of the solvent **(7a)** was obtained as colourless crystalline solid. yield 71 %, m.p. 243°C. Other compounds **(7 b-f)** were similarly prepared from **(4 b-f).**

(7a) 3-Amino-8-methyl –1H-3,4-dihydropyrazolo [3,4-b] quinolizin-4-one : yield 64%, m.p. 243°C; Calc : C, 55.81; H, 4.22; N, 32.54; O, 7.43 ;Found : C, 55.66; H, 4.34; N, 32.48; O, 7.56 ;IR (KBr) : 3455(NH),3340(NH_2),1650 (CO) cm^{-1}; NMR (DMSO-d_6)

13.7 (1H, s, NH), 7.28 (1H, d, = CH), 6.3 (1H, d, = CH), 5.77 (1H, q, = CH), 4.0 (2H, s, NH_2), 1.17 (3H, s, CH_3); MS(EI, 70 eV) : *m/z* 216.08 (12.7%).

(7b) 3-Amino-7-methyl –1H-3,4-dihydropyrazolo [3,4-b] quinolizin-4-one : yield 69%, m.p. 243°C; Calc : C, 55.81; H, 4.22; N, 32.54; O, 7.43 ;Found : C, 55.68; H, 4.38; N, 32.45; O, 7.59 ; IR (KBr) : 3460 (NH), 3330 (NH_2), 1625 (CO) cm^{-1}; NMR (DMSO-d_6) 13.7 (1H, s, NH), 7.28 (1H, d, = CH), 5.77 (1H, d, = CH), 5.0 (1H, s, = CH), 4.0 (2H, s, NH_2), 1.17 (3H, s, CH_3); MS(EI, 70 eV) : *m/z* 216.08 (12.7%).

(7c) 3-Amino-6-methyl –1H -3,4-dihydropyrazolo [3,4-b] quinolizin-4-one : yield 66%, m.p. 243°C; Calc : C, 55.81; H, 4.22; N, 32.54; O, 7.43 ;Found : C, 55.71; H, 4.32; N, 32.48; O, 7.60; IR (KBr) : 3450 (NH), 3360 (NH_2), 1643 (CO) cm^{-1}; NMR (DMSO-d_6) 13.7 (1H, s, NH), 7.06 (1H, s, = CH), 6.5 (1H, d, = CH), 5.2 (1H, d, = CH), 4.0 (2H, s, NH_2), 1.17 (3H, s, CH_3); MS(EI, 70 eV) : *m/z* 216.08 (12.7%).

(7d) 3-Amino-6-chloro–1 H -3,4-dihydropyrazolo[3,4-b]quinolizin-4-one : yield 70%, m.p. 181°C; Calc : C, 45.88; H, 2.57; Cl, 15.05; N, 29.72; O, 6.79 ; Found : C, 45.64; H, 2.49; Cl, 15.28; N, 29.65; O, 6.90; IR (KBr) : 3460 (NH), 3360 (NH_2), 1625 (CO), 740 (C-Cl) cm^{-1}; NMR (DMSO-d_6) 13.7 (1H, s, NH), 7.46 (1H, s, = CH), 6.5 (1H, d, = CH), 5.2 (1H, d, = CH), 4.0 (2H, s, NH_2); MS(EI, 70 eV) : *m/z* 236.03 (9.8%).

(7e) 6,8-Dibromo-3-amino–1 H -3,4-dihydropyrazolo [3,4-b] quinolizin-4-one : yield 69%, m.p.>300°C; Calc : C, 30.11; H, 1.40; Br, 44.52; N, 19.51; O, 4.46; Found : C, 30.49; H, 1.33; Br, 44.36; N, 19.80; O, 4.30 ; IR (KBr) : 3449(NH), 3294(NH_2), 1625 (CO),748 (C-Br) cm^{-1}; NMR (DMSO-d_6) 13.7 (1H, s, NH), 7.73 (1H, s, = CH), 6.9 (1H, s, = CH), 4.0 (2H, s, NH_2); MS(EI, 70 eV) : *m/z* 359.89 (9.8%).

(7f) 3-Amino-6-nitro–1 H -3,4-dihydropyrazolo [3,4-b] quinolizin-4-one : yield 78%, m.p.149°C; Calc : C, 43.91; H, 2.46; N, 34.14; O, 19.50;Found : C, 43.46; H, 2.32; N, 34.49; O, 19.41 ;IR (KBr) : 3500(NH), 3378(NH_2),1642 (CO), 1510 (NO_2) cm^{-1}; NMR (DMSO-d_6) 13.7 (1H, s, NH), 8.58 (1H, s, = CH), 6.5 (1H, d, = CH),5.2 (1H,d, = CH), 4.0 (2H, s, NH_2); MS(EI, 70 eV) : *m/z* 247.05 (12.1%).

General method for the preparation of 3-aminoisoxazolo[5,4-d]pyrido[1,2-a]pyrimidin-4(H)-one (8a-f)

Hydroxylamine hydrochloride (0.04 mole) was added to $NaOCH_3$ (0.06 mol) in absolute methanol (30 mL) and stirred for 10 min. 2-Methylthio-3-cyano-4-oxo-4H-pyrido[1,2-a]pyrimidine **(4a)** (0.01 mole) was added and the mixture was refluxed for 4-5

hr. Methanol was evaporated under reduced pressure and the residue was poured into ice-cold water. The solid separated was filtered, washed with diethyl ether and dried. Recrystallization from ethanol gave the analytically pure product **(8a)** as colourless crystals. yield 73 %, m.p. 202°C. Other compounds **(8 b~f)** were similarly prepared from **(4 b~f).**

(8b) 3-Amino-7-methyl-isoxazolo[5,4d]pyrido[1,2a]pyrimidin-4(*H*)-one : yield 68%, m.p. 202°C; Calc : C, 55.55; H, 3.73; N, 25.91; O, 14.80 ;Found : C, 55.41; H, 3.89; N, 25.80; O, 14.91 ;IR (KBr) : 3440,3380(NH_2), 1678(CO) cm^{-1}; NMR (DMSO-d_6) 7.28 (1H, d, = CH), 5.77 (1H, d, = CH), 5.0 (1H, s, = CH), 4.0 (2H, s, NH_2), 1.17 (3H, s, CH_3); MS(EI, 70 eV) : *m/z* 217.07 (11.0%).

(8c) 3-Amino-6-methyl-isoxazolo[5,4d]pyrido[1,2a]pyrimidin-4(*H*)-one : yield 62%; m.p. 202°C; Calc : C, 55.55; H, 3.73; N, 25.91; O, 14.80 ; Found : C, 55.37; H, 3.86; N, 25.78; O, 14.90 ; IR (KBr) : 3445,3375(NH_2), 1681(CO) cm^{-1}; NMR (DMSO-d_6) 7.06 (1H, s, = CH), 6.5 (1H, d, = CH), 5.2 (1H, d, = CH), 4.0 (2H, s, NH_2), 1.17 (3H, s, CH_3); MS(EI, 70 eV) : *m/z* 217.07 (11.0%).

(8d) 3-Amino-6-chloro-isoxazolo[5,4d] pyrido[1,2a]pyrimidin-4(*H*)-one : yield 61%, m.p. 241°C; Calc : C, 45.68; H, 2.13; Cl, 14.98; N, 23.68; O, 13.52 ;Found : C, 45.56; H, 2.06; Cl, 14.83; N, 23.72; O, 13.66 ; IR (KBr) : 3456, 3309(NH_2), 1627(CO), 748 (C-Cl) cm^{-1}; NMR (DMSO-d_6) 7.46 (1H, s, = CH), 6.5 (1H, d, = CH), 5.2 (1H, d, = CH), 4.0 (2H, s, NH_2); MS(EI, 70 eV) : *m/z* 237.01 (11.3%).

(8e) 6,8-Dibromo-3-amino-isoxazolo[5,4d]pyrido[1,2a]pyrimidin-4(*H*)-one : yield 69%, m.p. 235°C; Calc : C, 30.03; H, 1.12; Br, 44.40; N, 15.56; O, 8.89 ; Found : C, 30.22; H, 1.05; Br, 44.53; N, 15.82; O, 8.49 ; IR (KBr) : 3465, 3286(NH_2),1643(CO), 770 (C-Br) cm^{-1}; NMR (DMSO-d_6) 7.73 (1H, s, = CH), 6.9 (1H, s, = CH), 4.0 (2H, s, NH_2); MS(EI, 70 eV) : *m/z* 360.87 (11.3%).

(8f) 3-Amino-6-nitro-isoxazolo[5,4d]pyrido[1,2a]pyrimidin-4(*H*)-one : yield 70%; m.p. 185°C; Calc : C, 43.73; H, 2.04; N, 28.33; O, 25.89 ; Found : C, 43.59; H, 2.26; N, 28.14; O, 25.96 ; IR (KBr) : 3455, 3372(NH_2), 1643(CO), 1496(NO_2) cm^{-1} ; NMR (DMSO-d_6) 8.58 (1H, s, = CH), 6.5 (1H, d, = CH), 5.2 (1H, d, = CH), 4.0 (2H, s, NH_2); MS(EI, 70 eV) : *m/z* 248.04 (9.9%).

General method for the preparation of 4-amino-2,9-dimethylpyrido[1,2-a] pyrimido [4,5-d]pyrimidine-5(H)-one (9 a-f)

To a solution of sodium methoxide (0.04 mol) in methanol, acetamidine hydrochloride (0.02 mol) was added and the reaction mixture was stirred for 10-15 min. 2-Methylthio-3-cyano-4-oxo-4H- pyrido[1,2-a]pyrimidine **(4a)** (0.02 mol) was added and the mixture was refluxed for 6 hr. Methanol was evaporated under reduced pressure and the residue was poured into ice-cold water. The solid separated was filtered, washed with diethyl ether and dried. Recrystallization from ethanol gave the analytically pure product **(9a)** as colourless crystals yield 72 %, m.p. 255°C. Other compounds **(9 b-f)** were similarly prepared from **(4 b-f).**

(9a) 2-Amino-4,9-dimethylpyrido[1,2-a]pyrimido[4,5-d]pyrimidine-5(*H*)-one : yield 72% , m.p. 286°C; Calc : C, 59.74; H, 4.60; N, 29.03; O, 6.63 ;Found : C, 59.39; H, 4.78; N, 29.24; O, 6.44; IR(KBr) : 3460, 3360(NH_2), 1649 (CO) cm^{-1}; NMR (DMSO-d_6) 7.28 (1H, d, = CH), 6.3 (1H, d, = CH), 5.77 (1H, q, = CH), 4.0 (1H, s, NH_2), 2.35 (3H, s, CH_3), 1.71 (3H, s, CH_3); MS(EI, 70 eV) : *m/z* 242.10 (13.1%).

(9b) 2-Amino-4,8-dimethylpyrido[1,2-a]pyrimido[4,5-d]pyrimidine-5(*H*)-one : yield 64%, m.p. 286°C; Calc : C, 59.74; H, 4.60; N, 29.03; O, 6.63 ;Found : C, 59.40; H, 4.79; N, 29.22; O, 6.46 ;IR(KBr) : 3440, 3375(NH_2), 1645 (CO) cm^{-1}; NMR (DMSO-d_6) 7.28 (1H, d, = CH), 5.77 (1H, d, = CH), 5.0 (1H, s, = CH), 4.0 (1H, s, NH_2), 2.35 (3H, s, CH_3), 1.71 (3H, s, CH_3) MS(EI, 70 eV) : *m/z* 242.10 (13.1%).

(9c) 2-Amino-4,7-dimethylpyrido[1,2-a]pyrimido[4,5-d]pyrimidine-5(*H*)-one: yield 65% m.p. 286°C ; Calc : C, 59.74; H, 4.60; N, 29.03; O, 6.63 ;Found : C, 59.38; H, 4.81; N, 29.27; O, 6.42 ;IR(KBr) : 3450, 3380(NH_2), 1643 (CO) cm^{-1}; NMR (DMSO-d_6) 7.06 (1H, s, = CH), 6.5 (1H, d, = CH), 5.2 (1H, d, = CH), 4.0 (1H, s, NH_2), 2.35 (3H, s, CH_3), 1.71 (3H, s, CH_3); MS(EI, 70 eV) : *m/z* 242.10 (13.1%).

(9d) 2-Amino-7-chloropyrido[1,2-a]pyrimido[4,5-d]pyrimidine-5(*H*)-one : yield 67%, m.p. 217-218°C; Calc : C, 50.49; H, 3.08; Cl, 13.55; N, 26.76; O, 6.11 ;Found : C, 50.65; H, 3.35; Cl, 13.66; N, 26.94; O, 6.29 ; IR(KBr) : 3400, 3360(NH_2), 1697 (CO), 760(C-Cl) cm^{-1} ; NMR (DMSO-d_6) 7.46 (1H, s, = CH), 6.5 (1H, d, = CH), 5.2 (1H, d, = CH), 4.0 (1H, s, NH_2), 2.35 (3H, s, CH_3); MS(EI, 70 eV) : *m/z* 262.05 (12.0%).

(9e) 2-Amino-7,9-dibromopyrido[1,2-a]pyrimido[4,5-d]pyrimidine-5(*H*)-one : yield 71%, m.p. 235°C; Calc : C, 34.32; H, 1.83; Br, 41.51; N, 18.19; O, 4.16 ; Found :

C, 34.58; H, 1.74; Br, 41.25; N, 18.29; O, 4.05 ; IR(KBr) : 3460, 3309(NH_2), 1697 (CO), 717(C-Br) cm^{-1}; NMR (DMSO-d_6) 7.73 (1H, s, = CH), 6.9 (1H, s, = CH), 4.0 (1H, s, NH_2), 2.35 (3H, s, CH_3); MS(EI, 70 eV) : *m/z* 385.90 (13.8%).

(9f) 2-Amino-7-nitropyrido[1,2-a]pyrimido[4,5-d]pyrimidine-5(*H*)-one : yield 69% , m.p.279°C, Calc : C, 48.53; H, 2.96; N, 30.87; O, 17.63 ; Found : C, 48.44; H, 2.72; N, 30.39; O, 17.38 ; IR(KBr) : 3460, 3370(NH_2),1610 (CO), 1504(NO_2) cm^{-1}; NMR (DMSO-d_6) 8.58 (1H, s, = CH), 6.5 (1H, d, = CH), 5.2 (1H, d, = CH), 4.0 (1H, s, NH_2), 2.35 (3H, s, CH_3); MS(EI, 70 eV) : *m/z* 273.07 (12.1%).

RESULTS AND DISCUSSION

Pyrido [1, 2-a] pyrimidines were obtained by the cyclocondensation of cyanoketene S,S-acetal with substituted 2-aminopyridines. The reaction of cyanoketene S,S- acetal **(1)** with substituted 2-aminopyridine **(2a-f)** in presence of sodium ethoxide in boiling ethanol, afforded the corresponding ethoxy pyrido[1,2-a] pyrimidines **(3a-f)** in good yield. However, the reaction of **(1)** with substituted 2-aminopyridines **(2a-f)** in presence of triethylamine in refluxing dry benzene, formed **(4a-f) (Scheme : I)**. **4** underwent smooth displacement of SMe group with primary amines in ethanol to afford the corresponding amino substituted derivatives **(5a-f)** and **(6a-f) (Scheme II).** In an attempt to utilize the pyrido[1,2-a] pyrimidine **(4)** as a potential precursor in the preparation of fused heterocycles **(7), (8) and (9)**. it was reacted with various nucleophiles such as H_2N-NH_2, NH_2-OH and $CH_3C(=NH)NH_2$. **(4)** reacted smoothly with hydrazine hydrate in ethanol to afford the corresponding pyrimidine fused tricyclic derivatives **(7a-f) (Scheme II).** Tricyclic derivatives **(8a-f)** were obtained on reaction of **(4)** with hydroxyl amine. Similarly, compound **(9a-f)** was obtained on reaction of **(4)** with acetamidine hydrochloride in sodium methoxide and methanol **(Scheme II).** The formation of compounds **(3a-f)** and **(4a-f)** from **(2a-f)** while **(5a-f), (6a-f), (7a-f), (8a-f), (9a-f)** from **(4a-f)** was established on the basis of spectral and analytical data.

CONCLUSION

Present work shows that the amine function and the ring nitrogen of 2-aminopyridine are active sites for nucleophilic attack on α,β-unsaturated ketene dithioacetals. The direct displacement of the methyl thio group of ketene dithioacetals by amines provides a convenient method for the synthesis of pyrido[1,2-a] pyrimidines.

REFERENCES

1. M. Fawi, Abd El Latif , A. B. Magda, A. M. Aref and K. U. Sedek, Green Chemistry, **4**, 196 (2002).
2. I. Eljazi and Al-Afaleq, Synth. Commun., **31(22)**, 3557 (2001).
3. M. Augustin and N. J. Doelling, J. Prakt. Chem., **3**, 324 (1982).
4. Z. -T. Huang and X. Shi, Synthesis, 162 (1990).
5. R. Gompper and H. Schafer, Chem. Ber., **100**, 591 (1967).
6. S. Rajappa, R. Sreenivasan, B. G. Advani, R. H. Summervielle and R. Hoffmann, Indian J. Chem. Sect. B, **15**, 197 (1977).
7. S. Rajappa, M. D. Nair, R. Sreenivasan and B. G. Advani, Tetrahedron, **36**, 1673 (1982).
8. Z. -T. Huang and Z. -R. Liu, Synthesis, 357 (1987).
9. L. -B. Nang and Z. T. Huang, Synth. Commun., **26(3)**, 459 (1996).
10. J. -H. Zangh, M. -X. Nang and Z. -T. Huang, J. Chem. Soc. Perkin Trans I, 2087 (1999).
11. J. -H. Zangh; M. -X. Nang and Z. -T. Huang, J. Chem. Soc. Perkin Trans I, 321 (1999).
12. R. Gompper and N. Topfel, Chem. Ber., **95**, 2891 (1962).
13. X. Wang, X. Chen, H. Lian, Y. Pan and Y. Shi, Synth. Commun., 492 (1999).
14. S. H. Mashrequi and H. Harinarasubramanian, J. Chem. Research (S) 492 (1999).
15. G. H. Lee and C. S. Pak, Synth. Commun., **29(14)**, 2539 (1999).
16. Q. H. Zhang and J. Su, Synth. Commun., **29(20)**, 3497 (1999).
17. H. Junjappa, H. Ila and C. V. Ashokan, Tetrahedron, **46(16)**, 5423 (1990).

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