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CONVENIENT ROUTES FOR SYNTHESIS OF PYRIDOPYRIMIDINES AND POLYNITROGEN FUSED HETEROCYCLES

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ABSTRACT

Interaction of dimethyl-N-pyrimidine-formamidine derivatives **$2_{a,b}$** with the reagents 3 and 7 afforded the corresponding adducts **$6_{a,b}$** and **8**. The addition products **10** and **12** produced upon interaction of **2a,b** with dimedone and barbutric acids respectively. Treatment of **2a** with excess CS_2 yielded adduct **13**. Interaction of **2b** with acrylonitrile and methyl acrylate formed compounds **14** and **16**. Heterocycles **21a-c** and **22-24** produced via the reaction of **19** with different aromatic amines and amino reagents.

Keywords: Fused pyrimidines, pyridopyrimidine, N-dimethylpyrimidine formamidine, [4+2] cycloaddition reactions

INTRODUCTION

The pyrimidine framework is an important structure moiety present in various biologically active molecules including DNA and RNA.[1] So many naturally occurring and synthetic heterocycles containing pyrimidines and pyridopyrimidines posses valuable pharmacological properties.[2,3] Fused pyrimidine derivatives especially pyrido[2,3-d]pyrimidine, are well known for versatile biological activities like antimicrobial,[4] antifungal,[5] antitumor,[6] antiflammatory.[7] Other derivatives have been used as dihydrofloate reductase inhibitors.[8] Also some derivatives showed diuretic properties[9] activity against platelet aggregation,[10] analgesic activity,[11] and calcium channel antagonist.[9]

In light of the important biological properties of pyrimidines and pyridopyrimidine, the development of simple routes for synthesis of such structural motif represents an important area of our research.

In communication of our previous articles towards facile synthesis of pyridopyrimidines, and polynitrogen fused heterocycles[12-16], we thought to explore the utility of dimethyl pyridopyrimidine formamidine derivatives as a precursor for building a new type from these biologically active heterocycles. This work aims to explain simple routs for synthesis of biologically active substituted pyrimidines and fused pyridopyrimidines.

MATERIALS AND METHODS

All melting points are uncorrected and measured an electrothermal apparatus (Buchi 535, Switzerland) in an open capillary tube. IR spectra expressed in (cm^{-1}) were recorded in KBr pellets on a PA-9721 IR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were obtained on a Varian EM-390, 500 MHz, spectrometer in DMSO-d_6 as solvent, using TMS as internal reference and chemical shifts (δ) are expressed in ppm. Mass spectra were recorded on Kratos (75 eV) Ms Equipment. Elemental analyses were carried out by the microanalytical unit at National Research Centre, Giza, Egypt. All reactions were monitored by thin layer chromatography, carried out on 0.2 mm silica gel 60 F-254 (Merck) plates using UV light (245 and 365 nm) for detection.

Column chromatography was carried out on a Baker silica gel powder (60–200 mesh).

General procedure: Synthesis of 6a and 6b:
To a suspension of 2a and /or 2b (0.33 or 0.198 gm, 0.001 mol), added ethyl acetoacetate (0.13 ml, 0.001 mol), in (15ml) DMF / 1 ml of glacial acetic acid. The reaction mixture was heated under reflux for 72 h. After cooling, the excess solvent was removed under reduced pressure. The residue was chromatographed (Silica gel, 60 mesh), with ethyl acetate: benzene (8:2, v/v).

2-(6-acetyl-5-oxo-1-phenyl-2-thioxo-2,3,5,8-tetrahydro-1H-pyrido-[2,3-d] pyrimidine-4-ylidene)-malononitrile (6a).
Pale yellow oil, yield (40%); Ms (EI) m/z (%) 361 [M^+, 37.2 %]; IR (KBr, cm^{-1}): 3421, 3385 (2NH); 2918 (CH_3); 2204 (CN); 1689, 1637 (2C = O); ^{1}H-NMR (500 MH_z, DMSO-d_6, TMS): δ 1.60 (s, 3H, CH_3); 6.60 (s, 1H, CH -7 of pyridine); 7.20-7.82 (m, 5H, aromatic protons); 8.50, 10.8 (2s, 2H, 2NH, D_2O exchangeable). Anal. Calcd. For M.F: $C_{18}H_{11}N_5O_2S$: C, 59.62; H, 3.07; N, 19.80; S, 8.87. Found: C, 59.50; H, 3; N, 19.50; S, 8.75.

6-acetyl-5-oxo-1-phenyl-2-thioxo-2,3-dihydro-1H,8H-pyrido-[2,3-d]pyrimidine-4,5-dione (6b).
Brown oil, yield (30%); Ms (EI) m/z (%): 237 [M^+, 45 %]; IR (KBr, cm^{-1}): 3420, 3380, 3158 (3NH); 2920 (CH_3); 1685, 1635, 1660 (3 C=O); ^{1}H-NMR (500 MH_z, DMSO-d6, TMS): δ 1.25 (s, 3H, CH_3); 6.60 (s, 1H, CH-7 of pyridine); 9.80 (s, 1H, NH, D_2O exchangeable); 11.60 (s, 1H, NH, D_2O exchangeable); 12.80 (s, 1H, NH, D_2O exchangeable). Anal; Calcd. For M.F: $C_9H_7N_3O_3S$: C, 45.57; H, 2.97; N, 17.71; S, 13.52. Found: C, 45.53; H, 2.95; N, 17.50; S, 14.49.

General procedure: Synthesis of 8, 10 and 12:
To a solution of dimethylpyridine formamidine 2a (0.001 mol) added ω- cyanoacetate (0.001 mol), 5,5 dimethyl cyclohexan – 1,3- dione (0.001 mol), and /or barbutric acid (0.001 mol), in (15 ml) of DMF / 1 ml of glacial acetic acid. The mixture was refluxed for 72h., until the starting materials had disappeared as indicated by TLC. The solvent was poured onto ice/water, the obtained solids crystallized from DMSO.

2-(6-benzoyl-5-amino-1-phenyl-2-thioxo-2,3,5,8-tetrahydro-1H-pyrido-[2,3-d] pyridine-4-ylidene)-malononitrile (8):
White crystals, m.p. 290-92ºC, yield (62%); Ms (EI) m/z (%) 421 [M^+, 60.40 %]; IR (KBr, cm^{-1}): 3152 - 3160 (br, NH); 3126 - 3120 (CH, 2 Ph); 1690, 1678 (C=C); 1660 (C = O); ^{1}H-NMR (500 MHz, DMSO-d_6, TMS): δ 6.9 (s, 1H, CH-7 of pyrimidine); 7.26 - 7.80 (m, 10 protons of 2Ph); 8.60 (s, 1H, NH, D_2O exchangeable); 8.90, 12.10 (2s, 2NH, D_2O exchangeable). ^{13}C-NMR (500 MHz, DMSO-d_6, TMS): δ 53.90 (CN-<u>C</u>-CN), 76.30 (C-9), 104 (C-6), 116.80 (<u>C</u>≡N), 124, 125, 128.5, 129.5, 130, 134, 136, 139 (aromatic carbons), 1414.50 (C-7), 143 (C-10), 163 (C-S), 177.90 (C=S), 186 (<u>C</u>=C), 198 (C=O) Anal. Calcd. For M.F: $C_{23}H_{13}N_6OS$: C, 65.39; H, 3.34; N, 19.89; S, 7.59. Found: C, 65.20; H, 3.30; N, 19.85; S, 7.53.

2-(6-[4,4-dimethyl-2,6-dioxo-cyclohexamethylene)-amino]-1-phenyl-2-thioxo-2,3-dihydro-1H-pyrimidine-4-ylidene)- malononitrile (10):
Buff crystals, m.p. 310-12ºC, yield (53%); Ms (EI) m/z (%) 418 [M^+, 42 %]; IR (KBr, cm^{-1}): 3158 (NH); 2920, 2859 ($2CH_3$); 2208 (CN); 1700,1680 (2C = O); 1595 (C=N); ^{1}H-NMR (500 MH_z, DMSO-d_6, TMS): δ 0.90, 1.20 (2s, 6H, $2CH_3$); 1.90, 2.30 (2s, 4H, $2CH_2$ of dimedone); 6.20 (s, 1H, C-H_5 of pyrimidine); 7.20 -7.90 (m, 5H, aromatic protons); 8.10 (d, 1H, N=CH); 8.90 (s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (500 MH_z, DMSO-d_6, TMS): δ 26 (-CH_3), 52.90 (-<u>C</u>H_2 dimedone), 54.0 (<u>C</u>-CN). 65 (<u>C</u>H, dimedone), 97 (C-S), 118 (<u>C</u>≡N), 124, 126, 128, 139 (aromatic carbones), 147 (C-6), 164 (<u>C</u>=N), 177.5 (C=S), 185 (C-4), 208 (2C=O). Anal. Calcd. For M.F: $C_{22}H_{20}N_5O_2S$: C, 63.29; H, 4.59; N, 16.78; S, 7.68. Found: C, 63.15; H, 4.55; N, 16.75; S, 7.62.

2-(1-Phenyl-2-thioxo-6-[2,4,6-trioxo-hexahydro-pyrimidine-5-yl-methylene)-amino]-2,3-dihydro-1H-pyrimidine-4-ylidene)-malononitrile (12):
White crystals, m.p. 305-7ºC, yield (40%); Ms (EI) m/z (%) 405 [M^+, 8.0 %]; IR (KBr, cm^{-1}): 3426 (br, NH); 3150 (NH); 3028 (C=H aromatic); 2210 (CN); 1710, 1690, 1670 (3C= O); 1592 (C=N); ^{1}H-NMR (500 MH_z, DMSO-d_6, TMS): δ 3.80 (d, 1H, barbutric C-H); 5.60 (s, 1H, C-H_5 of pyrimidine); 7.70 (m, 5H Ph protons); 8.10 (d, 1H, CH=N); 8.90 (s, 1H, NH, D_2O exchangeable); 10.40, 10.60 (2s, 2H, 2NH, D_2O exchangeable) Anal. Calcd. For M.F: $C_{18}H_{11}N_7O_3S$: C, 53.33; H, 2.73; N, 24.19; S, 7.91. Found: C, 53.30; H, 2.50; N, 24.0; S, 7.89.

2-(2-dimethyamino-4,7dithioxo-,4,6,7,8-tetrahydro-pyrimido[4,5-d][1,3]-thiazin-5-ylidene)-malononitrile (13):
To a solution of 2a (0.001mol), in 15 ml DMF/5ml KOH (10%), (1 ml) glacial acetic acid, and carbon disulphide (excess), were added. The reaction mixture was heated for 48h. Cooled, then poured onto ice/water, the obtained oil was chromatographed

(Silica gel, 60 mesh.) with ethylacetat-benzene (8:2, v/v).

Yellow oil, yield (62%); Ms (EI) m/z (%) 396 [M^+, 30 %]; IR (cm^{-1}): 3327, 3290 (2 NH); 2958, 2922 ($2CH_3$); 2206 (CN); 1616 (C=C), 1598 (C=N); ^{1}H-NMR (500 MH_z, $CDCl_3$): δ 2.20, 2.40 (2s, 6H, 2 CH_3); 7.10 – 7.40 (m, 5H, aromatic protons); 8.70 (s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (500 MH_z, $CDCl_3$): δ 34.20 ($2CH_3$), 117.40 (C≡N), 124, 125, 128, 139 (aromatic carbons), 160 (C-7), 176 (C=S), 186.20 (C-4), 217.30 (C=S, pyridine ring). Anal. Calcd. For M.F: $C_{17}H_{12}N_6S_3$: C, 41.23; H, 2.52; N, 26.23; S, 30.02. Found: C, 41.20; H, 2.50; N, 26.20; S, 30.

4-oxo-2-thioxo-1,2,3,4-tetrahydro–pyrido[2,3-d]pyrimidine-5-cabonitrile (14).

A mixture of 2b (0.001 mol), acrylonitrile (0.05 ml) in (15 ml) of DMF and (1 ml) of glacial acetic acid, were heated under reflux for 72 h. After Cooling poured onto ice/water, the solid so formed was crystallized from DMSO.

Buff crystals, m.p. 278 -80 ºC, yield (32%); Ms (EI) m/z (%) 204 [M^+, 5.6 %]; IR (KBr, cm^{-1}): 3270 (NH); 3320 (NH); 2210 (CN); 1700 (C=O); 1610 (C=C); 1595 (C=N); ^{1}H-NMR (500 MH_z, DMSO-d_6, TMS): δ 7.30 (d of d, *J* = 8.40, 1H, C-H_6 of pyridine); 8.60 (d of d, *J* = 8.40, 1H, C-H_7 of pyridine); 9.30, 11.20 (2s, 2H, 2NH, D_2O exchangeable). ^{13}C-NMR (500 MH_z, DMSO-d_6, TMS): δ 116 (C-6), 117.20 (C-9), 118.60 (C≡N), 149 (C-7), 166 (C-10), 170 (C=O), 184 (C=S). Anal; Calcd. For M.F: $C_8H_4N_4OS$: C, 47.05; H, 1.97; N, 27.44; S, 15.07. Found: C, 47.0; H, 1.95; N, 27.30; S, 15.0.

5–acetyl–2-thioxo–2,3–dihydro–1*H*-pyrido[2,3-d]–pyrimidine–4-one (16).

A mixture of 2a (0.001 mol) and methylacrylate (0.086 ml) was added to (15 ml) of DMF and (1 ml) glacial acetic acid. The reaction mixture was worked up in a similar manner as described above.

White crystals, m.p. 275 -76 ºC, DMSO, yield (25%); Ms (EI) m/z (%) 221 [M^+, 25%]; IR (KBr, cm^{-1}): 3368 (NH); 3318 (NH); 2208 (CN); 1700 (C=O); 1690 (C=O); 1610 (C=C); 1598 (C=N); ^{1}H-NMR (500 MH_z, DMSO-d6, TMS): δ 2.30 (s, 3H, CH_3); 4.00 (s, 1H, NH of pyrimidine); 7.50 (d, 1H, C-H_6 of pyridine); 8.90 (d, 1H, C-H_7 of pyridine); 9.57 (s, 1H, NH, D_2O exchangeable), 11.30 (s, 1H, NH, D_2O exchangeable). Anal. Calcd. For M.F: $C_9H_7N_3O_2S$: C, 48.86; H, 3.19; N, 18.99; S, 14.59. Found: C, 48.85; H, 3.16; N, 18.80; S, 14.53.

N\-[5-4(chloro-phenyl)-6-cyano-4-oxo-2-thioxo-1,2,3,4,5,8-hexahydro-pyrido[2,3-d]-pyrimidine-7-yl]-N-N-dimethyl-formamidine. (19)

A mixture of compound 18 (0.001 mol) and dimethyl formamide dimethyl acetal (5 ml) was heated at 120-130 ºC for 1h. (oil bath). After cooling, the obtained solid was crystallized from DMSO.

Yellow crystals, m.p. 285 -86 ºC; yield (80%); Ms (EI) m/z (%) 363 [M^+ +2, 13%]; 361 [M^+, 40%], IR (KBr, cm^{-1}): 3350, 3320, 3280 (3NH); 2950, 2920 ($2CH_3$); 1670 (C=O); 1595 (C=N); ^{1}H-NMR (500 MH_z, $CDCl_3$): δ 2.41 (2s, 6H, $2CH_3$); 3.70 (s, 1H, NH of pyridine, D_2O exchangeable); 3.90 (s, 1H, CH of pyridine); 4.20 (s, 1H, CH of pyridine); 4.60 (s, 1H- NH of pyrimidine, D_2O exchangeable); 7.0 - 7.15 (m-4H of aromatic protons); 7.50 (s, 1H of N=C- H); 8 (s, 1H, NH of pyrimidine, D_2O exchangeable). Anal. Calcd. For M.F: $C_{16}H_{16}ClN_5OS$: C, 53.11; H, 4.46; Cl, 9.80; N, 19.35; S, 8.86. Found: C, 53.0; H, 4.43; Cl, 9.70; N, 19.20; S, 8.83.

General procedure:

Synthesis of 21a and 21b:

To a suspension of compound **19** (0.3099, 0.001 mol) in (20 ml) of glacial acetic acid, aniline and/or p-promoaniline were added. The reaction mixture was heated under reflux for 15h., cooled, the solids was crystallized from toluene.

10-(4-chlorophenyl)-5-phenylimino-2-thioxo-2,3,5,6,9,10-hexahydro-1H-1,3,6,8,9-pentaza-anthracene-4-one. (21a)

Yellow crystals, m.p. 260 -61 ºC; yield (40%); Ms (EI) m/z (%) 436 [M^++2, 6.30 %]; 434 [M^+, 18.2%]; 402 [M^+-S, 100%]; IR (KBr, cm^{-1}): 3270, 3187, 3180 (3NH); 1716 (C=O); 1620 (C=C); ^{1}H-NMR (500 MH_z, DMSO-d6, TMS): δ 3 (1s, 1H, NH of pyrimidine); 3.98 (1s, 1H, pyridine proton); 7.0 (s, 1H, N=CH of pyrimidine,); 7.5 (m, 5H, of aromatic protons + 1H of pyridine); 7.60 – 7.70 (m, 4H, aromatic protons); 10.00 (s, 1H, NH, D_2O exchangeable); 11.60 - 12 (br, 2H, 3NH, D_2O exchangeable). ^{13}C-NMR (500 MH_z, DMSO-d6, TMS): δ 21.50 (C-10), 87.20 (C-C=O), 92.80 (C-C=N), 122, 127, 128.70, 129.5, 130.5, 135.7, 148.8 (aromatic carbons), 140 (N-C-NH), 152.80 (NH-C-NH), 162 (C-7), 164 (C-5), 165 (C=N), 180 (C=O), 183.5 (C=S) Anal. Calcd. For M.F: $C_{21}H_{15}ClN_6OS$: C, 58.00; H, 3.48; Cl, 19.32; N, 8.15; S, 7.37. Found: C, 57.80; H, 3.46; Cl, 19.30; N, 8.12; S, 7.35.

5-(4-bromo-phenylimino)-10-(4-chlorophenyl)-2-thioxo-2,3,5,6,9,10-hexahydro-1H-1,3,6,8,9-pentaza-anthracene-4-one (21b).

Yellow crystals, m.p. 202-204 ºC; yield (40%); Ms (EI) m/z (%) 516 [M^++4, 11%] 514 [M^+ +2, 40%]

512 [M^+ 29%]; IR (KBr, cm^{-1}): 3275, 3195, 3180 (3NH); 1714 (C=O); 1625 (C=C aromatic); ^{1}H-NMR (500 MH_z, DMSO-d6, TMS): δ 3.00 (s, 1H, NH of pyrimidine); 3.80 (s, 1H, pyridine proton); 7.30- 7.60 (m, 5H, N=CH of pyrimidine + 5H of aromatic protons); 7.70-8.30 (m, 4 H of aromatic protons); 11.60-12.00 (br, 2H, 2NH, D_2O exchangeable). Anal. Calcd. For M.F: $C_{21}H_{14}BrClN_6OS$: C, 49.09; H, 2.75; Br, 15,55; Cl, 6.90; N, 16.36; S, 6.24. Found: C, 49.00; H, 2.55; Br, 15.50; Cl, 6.82; N, 16.20; S, 6.20.

General procedure:

Synthesis of 22, 23 and 24:
To a solution of compound **19** (0.001 mol) in (20 ml) of glacial acetic acid, methyl amine, hydrazine hydrate and/or phenyl hydrazine (0.001 mol), were added. The reaction mixture was heated under reflux for 48h., until the starting material had disappeared by TLC. Cooled, the obtained solid was filtered off, crystallized from ethanol.

10-(4-chlorophenyl)-5-methylimino-2-thioxo-2,3,5,6,9,10-hexahydro-1H-1,3,6,7,9-pentaza-anthracene-4-one. (22)
Grey crystals, m.p. 270 -72 ºC; yield (50%); Ms (EI) m/z (%) 374 [M^+ +2, 6.30%]; 372 [M^+, 18.2%]; IR (KBr, cm^{-1}): 3361, 3317, 3297 (3NH); 1716 (C=O); 1624 (C=C aromatic); ^{1}H-NMR (500 MH_z, DMSO-d6, TMS): δ 1.88 (s, 3H, CH_3); 3.03 (s, 1H, NH of pyrimidine); 4.02 (s, 1H, NH, D_2O exchangeable); 4.40 (s, 1H, CH-5 of pyridine); 7.06 (s, 1H, CH-8 of pyrimidine); 7.20 (d, 2H, J_{H-H}= 10 Hz, aromatic), 7.50 (d, 2H, J_{H-H} = 10.20 Hz, aromatic), 7.80 (s, 1H, NH, D_2O exchangeable); 11.93 (s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (500 MH_z, DMSO-d6, TMS): δ 21.60 (C-10), 28.50 (CH_3), 81.80 (C-C=O), 92 (C-C=N), 128.30, 130, 131, 135.5 (aromatic carbons), 140 (NH-C-N), 152.50 (NH-C-NH), 162 (C-7), 164 (C-5), 168 (C=O), 182 (C=S). Anal. Calcd. For M.F: $C_{16}H_{13}ClN_6OS$: C, 51.54; H, 3.51; Cl, 9.51; N, 24.54; S, 8.60. Found: C, 51.40; H, 3.43; Cl, 9.40; N, 24.50; S, 8.45.

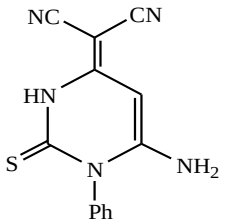
10-(4-chloro-phenyl)-5-hydrazono-2-thioxo-2,3,5,6,9,10-hexahydro-1H-1,3,6,7,9-pentaza-anthracene-4-one (23).
White crystals, m.p. 295 -96 ºC; yield (60%); Ms (EI) m/z (%) 375 [M^+ +2, 4.8 %]; 373 [M^+, 15%]; 357 [M^+- NH_2]; IR (KBr, cm^{-1}): 3427 (NH_2); 3317, 3300, 3270, 3220 (4NH); 1715 (C=O); 1620 (C=C aromatic); 1580 (C=N); ^{1}H-NMR (500 MH_z, DMSO-d6, TMS): δ 3.20 (s, 1H, NH of pyrimidine, D_2O exchangeable); 4.03 (s, 1H, NH D_2O exchangeable); 4.30 (s, 1H, CH-5 of pyridine); 7.2 (s, 1H, CH-8 of pyrimidine); 7.52-8.02 (m, 5H, 4 aromatic protons + 1H, NH, D_2O exchangeable); 8.52 (s, 2H, NH_2, D_2O exchangeable); 11.30 (s, 1H, NH, D_2O exchangeable). Anal. Calcd. For M.F: $C_{15}H_{12}ClN_7OS$: C, 48.19; H, 3.29; Cl, 9.84; N, 6.23; S, 8.58. Found: C, 48.12; H, 3.25; Cl, 9.82; N, 6.20; S, 8.53.

10-(4-chloro-phenyl)-5-(phenyl-hydrazono)-2-thioxo-1,3,5,6,7,10-hexahydro-1H-1,3,6,8,9-pentaza-anthracene-4-one (24).
Pale yellow crystals, m.p. 312 -14 ºC; yield (25%); Ms (EI) m/z (%) 451 [M^+ +2, 8.0 %]; 449 [M^+, 24.20%]; IR (KBr, cm^{-1}): 3394, 3327 (2NH); 3290-3270 (br, 2NH); 1700 (C=O); ^{1}H-NMR (500 MH_z, DMSO-d6, TMS): δ 3.4 (s, 1H, NH of pyrimidine, D_2O exchangeable); 4.0 (s, 1H, NH D_2O exchangeable); 4.20 (s, 1H, CH-5 of pyridine); 7.21 (s, 1H, CH-8 of pyrimidine); 7.30 (d, 2H, J_{H-H}= 10.40 Hz, aromatic), 7.50 (d, 2H, J_{H-H} = 10.30 Hz, aromatic), 7.70 (s, 1H, NH, D_2O exchangeable); 8.29- 8.53 (m, 6H, 5 aromatic protons + 1H, NH, D_2O exchangeable); 11.51 (s, 1H, NH, D_2O exchangeable). Anal. Calcd. For M.F: $C_{21}H_{15}ClN_7OS$: C, 56.06; H, 3.58; Cl, 7.88; N, 21.79; S, 7.13. Found: C, 56.0; H, 3.50; Cl, 7.84; N, 21.75; S, 7.0.

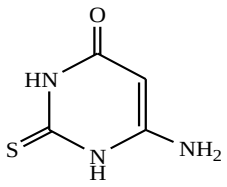
RESULTS AND DISCUSSION

6-(amino-1-phenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-ylidene)malo- nonitrile **1a**[17] and 6-amino-2-thioxo-1-*H*-pyrimidin-4-one **1b**[18] were allowed to react with dimethyl formamide dimethyl acetal (DMFDMA) to form the corresponding pyrimidin-4-yl formamidine derivatives **2a,b** (Scheme 1).

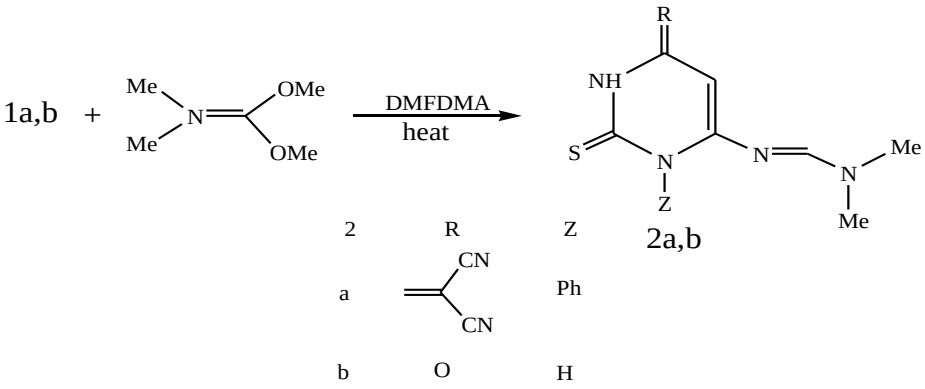
Compound **2a** was examined previously by our group as stabilizing agent for polyvinyl chloride, (PVC)[19] and showed a higher antibacterial and antifungal activities which encouraged us to utilize **2a,b** as a starting material for synthesis of fused pyrimidines.



1a



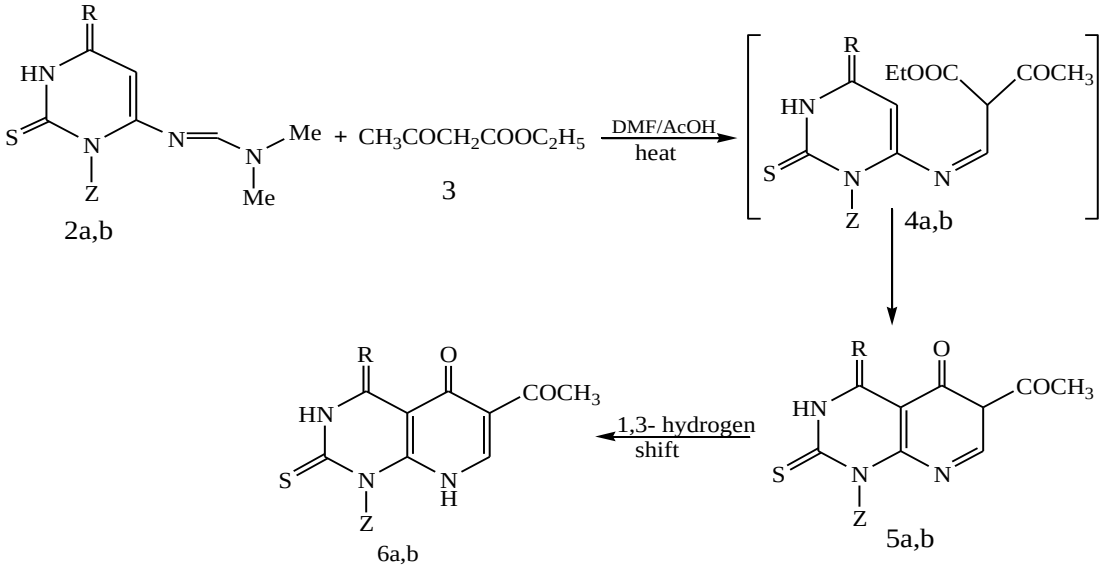
1b

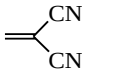


2	R	Z
a		Ph
b	O	H

Scheme1

Interaction of dimethylpyrimidine formamidines **2a,b** with ester active methylene reagent **3** (ethyl aceto acetate) in DMF/AcOH under reflux produced the fused pyridopyrimidines **6a,b** respectively(Scheme2).



2 - 6	R	Z
a		Ph
b	O	H

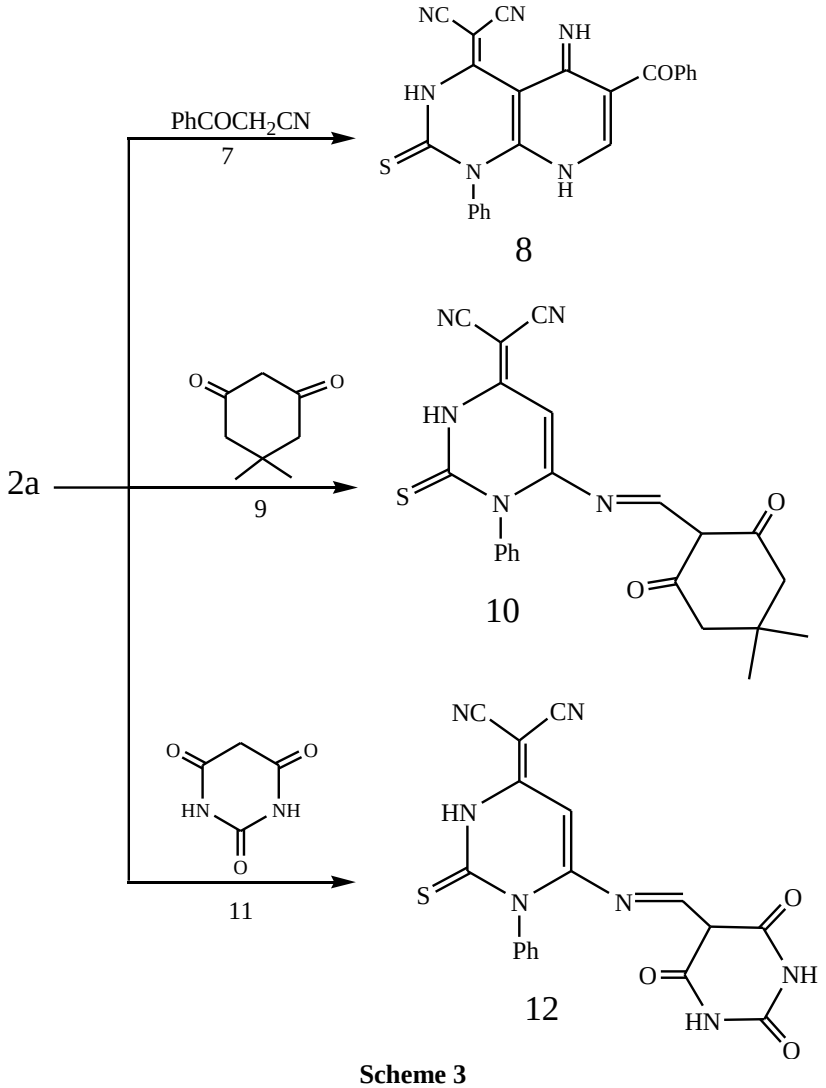
Scheme 2

The ^{1}H-NMR spectra of the adduct **6a** taken as example showed the disappearance of the characteristic signal of pyrimidine *H*5 which appear at δ = 6.60 ppm. Also it showed the presence of a signal at δ = 1.60 ppm that attributed to the acetyl methyl group and two signals at δ = 8.50 ppm and 10.80 for 2NH groups. Regarding to the *IR* spectrum of **6a**, it revealed two bands at ν = 1698, 1637 cm^{-1} for the carbonyl groups.

It is believed that the addition of the active methylene reagent led to the formation of the intermediate **4a,b** at first followed by cyclization via loss of ethanol to yield compounds **5a,b**. The latter were converted to the final adducts **6a,b** through 1,3 hydrogen shift. All the analytical and spectroscopic data were in agreement with the structure of the suggested products (c.f. experimental section).

Similarly **2a** reacted with ω-cyano-acetophenone to produce the corresponding pyridopyrimidine derivative **8** (Scheme 3).

On the other hand studying the behavior of **2a** with cyclic active methylene reagent like 5,5-dimethyl cyclohexan-1,3-dione **9** and barbutric acid **10** produced the addition products **11** and **12** respectively (Scheme 3).



Scheme 3

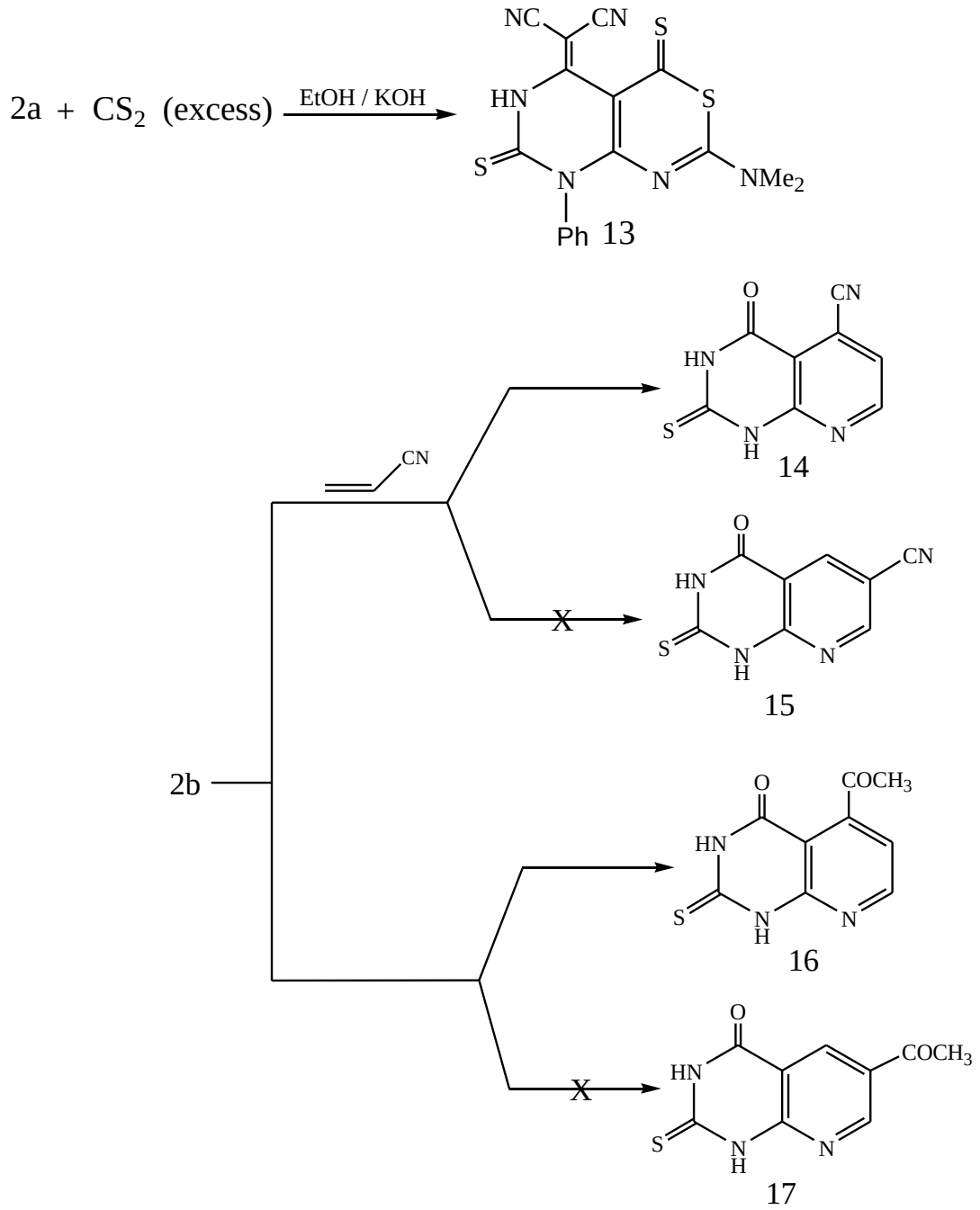
The ^{1}H-NMR spectra of both adducts **10, 12** revealed the existence of singlet signals at δ = 6.20 and 5.60 ppm respectively for pyrimidine *H*5 beside the other characteristic signals (c.f. experimental section).

The *IR* spectrum of product **10** revealed two bands at ν = 2920, 2859 cm^{-1} for two methyl groups and other two bands at ν = 1700, 1680 cm^{-1} attributed to the carbonyl groups.

For more studying to the chemical behavior of **2a**, it was allowed to react with excess carbon disulfide in alcoholic/KOH solution under reflux to form the corresponding fused adduct **13** (Scheme 4).

The spectroscopic data proved the formation of such product without loss of the -NMe_2 group of the aza-methine bridge and the ^{1}H-NMR revealed its existence at δ = 2.20, 2.40 ppm (c.f. experimental section).

Continuously to the aim of the report, N-dimethyl pyrimidine – formamidine **2b** was reacted with acrylonitrile and methyl-acrylate. [4+2] cyclo addition reaction took place to afford the pyrido[2,3–d]pyrimidines **14** and **16** respectively (Scheme 4).

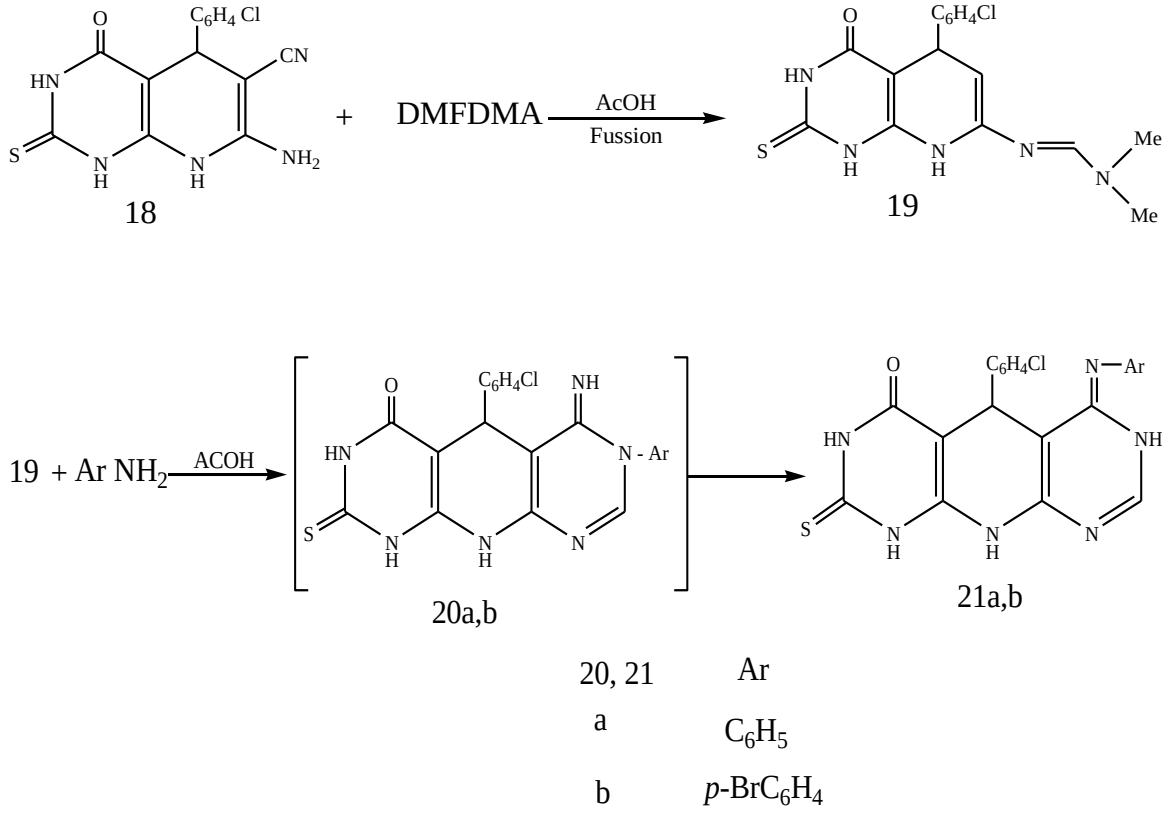


Scheme 4

It is assumed that [4+2] cycloaddition initially occurred that was followed by dimethylamine elimination. This would lead to **14** and **16** or their isomeric **15** and **17**. Structure of **14** and **16** was established based on ^{1}H-NMR for example ^{1}H-NMR spectra of compound **14** revealed doublet that typical to *H*6 and *H7* adjacent to each other, this value is different than the expected value for *H*5 and *H7* respectively.[20]

For synthesis of different polynitrogen fused heterocycles, amino pyrido[2,3–d]pyrimidine **18**[14] was converted to its aza-enamine derivative **19** by fusion with DMFDMA in oil bath. The structure of **19** was confirmed with spectroscopic data (c.f. experimental section).

The azaenamine **19** was allowed to react with different aromatic amines in acetic acid to form the fused adducts **21a–c** (Scheme 5).

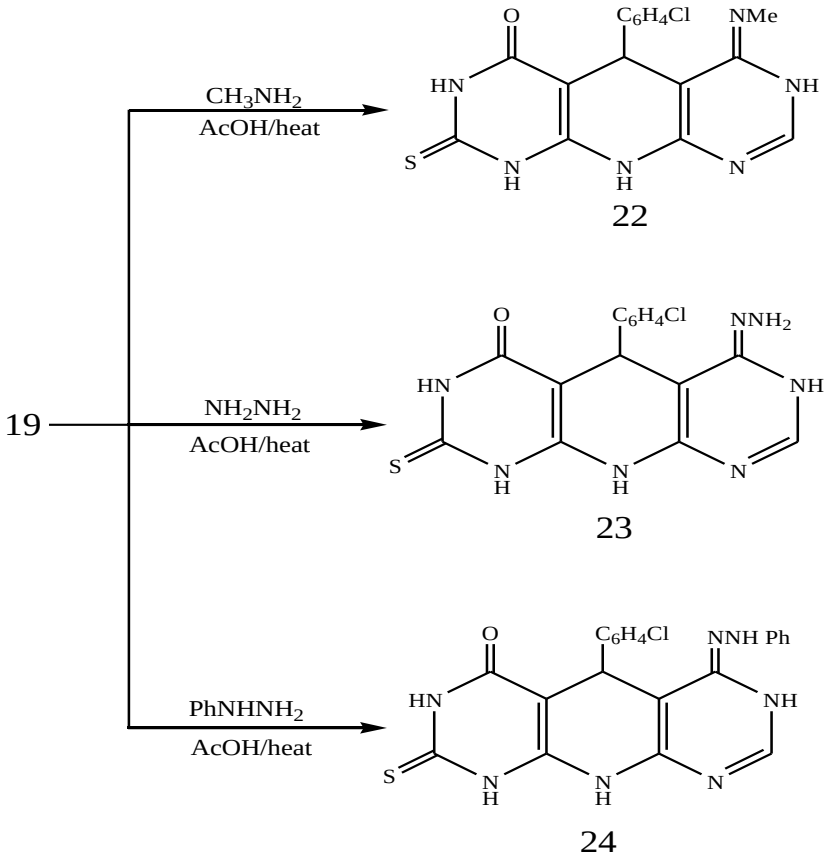


20, 21	Ar
a	C_6H_5
b	*p*-BrC_6H_4

Scheme 5

The structure of **21a,b** was established by analytical and spectroscopic data. IR spectrum of **21a** which was considered as example exhibited the disappearance of the methyl and cyanide bands and the existence of -*NH* band at ν = 3270 cm^{-1}. The ^{1}*H*-NMR spectrum of **21a** showed singlet signal at δ = 7.10 ppm for the proton of new fused pyrimidine ring.

On the other hand interaction of **19** with methyl amine, hydrazine hydrate and phenyl hydrazine produced the corresponding fused adducts **22–24** (Scheme 6). The suggested structure of **22–24** was established via the spectroscopic data (c.f. experimental section). The formation of such polynitrogen heterocycles was occurred through nucleophilic substitution on the aza-methylidene carbon followed by cyclization to afford the imino derivatives **22-24**. The latter underwent Dimorth rearangment[21] to yield the final thermodynamically more stable adducts **22-24** (Scheme 6).



Scheme 6

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