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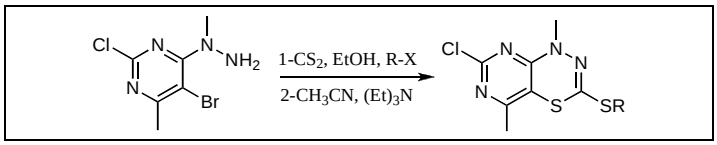

5-Bromo-2-chloro-4-methyl-6-(1-methylhydrazino)pyrimidine is readily obtained from the recently reported 5-bromo-2,4-dichloro-6-methylpyrimidine by treatment with methylhydrazine in chloroform. Treatment of this compound with carbon disulfide and several alkyl halides gave an intermediate which was successfully converted to its corresponding 3-(alkylsulfanyl)-7-chloro-1,5-dimethyl-1*H*-pyrimido[4,5-*e*][1,3,4]thiadiazine derivatives in basic acetonitrile. The latter compounds were reacted with secondary amines in boiling ethanol to afford the related 7-amino derivatives.

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INTRODUCTION

Our interest in pyrimido[4,5-*e*][1,3,4]thiadiazine synthesis emerges from few reports on their diverse biological activities. These compounds have been described as being nucleoside analogues [4,5], antiinflammatory, hypotensive, diuretic [1,2], and phosphodiesterase inhibitor [2] agents. Despite their importance from pharmacological and synthetic point of views, comparatively few methods for their preparation have been reported.

Pyrimido[4,5-*e*][1,3,4]thiadiazines have been solely synthesized from pyrimidines. Previous routes to such systems have involved condensation of 2,4-dichloro-5-nitro-6-methylpyrimidine with dithizone [6] *via* Smiles Rearrangement (Figure 1), heterocyclization of 6- hyrazinosubstituteduracils with isothiocyanates and *N*-bromosuccinimide [1-5] (Figure 2), reaction of thiohyrazides with 4,5- dihalopyrimidines [7] and cyclocondensation of thiosemicarbazide with 5-bromobarbituric acid [8](Figure 3).

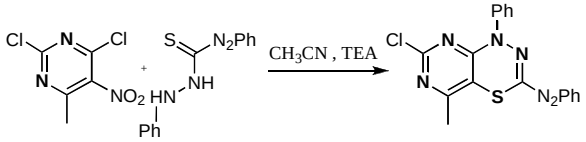
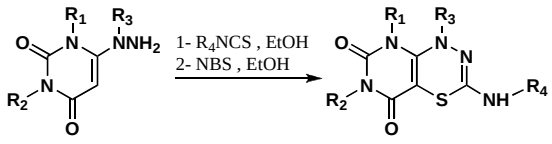


Figure 1



R1, R2, R3 = H, variety alkyl groups
R4 = alky aryl and sugar groups

Figure 2

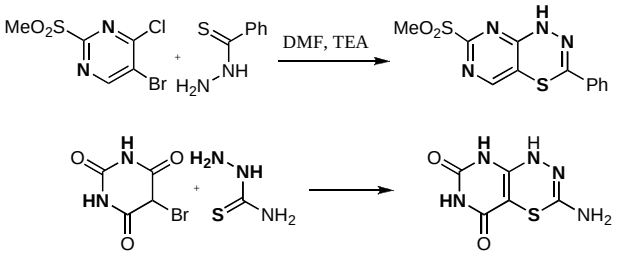


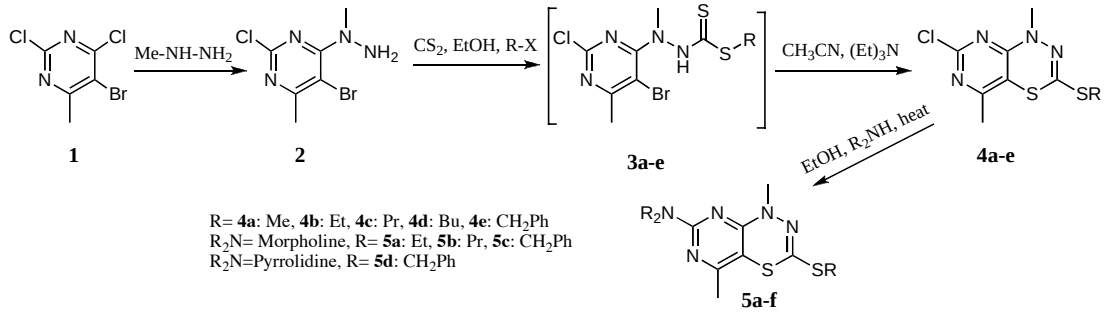
Figure 3

The current route is also based upon intramolecular heterocyclization of new hydrazinecarbodithioate derivatives **3 a-e** (Scheme I) The latter compounds were easily synthesized from the new 5-bromo-2-chloro-4-methyl-6-(1-methylhydrazino)pyrimidine (**2**) which in turn is readily obtainable from 5-bromo-2,4-dichloro-6-methylpyrimidine [9].

RESULTS AND DISCUSSION

5-Bromo-2-chloro-4-methyl-6-(1-methylhydrazino)-pyrimidine **2** was reacted with carbon disulfide and several alkyl halides in basic ethanol to afford the key intermediates hydrazinocarbodithioates **3a-e**. These intermediates, which are air sensitive, were subjected to intramolecular heterocyclization in basic acetonitrile without further purification to give the cyclized products **4a-e**. The latter compounds were further reacted with secondary amines to give the amino derivatives **5a-d**.

The structure of new derivatives **4a-e** and **5a-d** were confirmed by their spectral and microanalytical data. For example, the IR spectrum of **4a** was devoid of the stretching vibration bands at 3280 and 3360 cm^{-1} due to NH_2 functionality of the precursor 2 but exhibits vibration bands at 800, 2900, 2940 cm^{-1} due to 7-chloro and methyl groups respectively. The ^1H NMR spectrum of **4a** was



also devoid of the broad NH_2 signal at δ 4.2 ppm of the precursor but showed a singlet at δ 2.41 ppm assignable to 3 protons for the SMe group which indicates the formation of compound **4a**. The molecular ions of **4a** (M: M+2) was observed at 260 and 262 (60%:20%) corresponding to the molecular formula $C_8H_9ClN_4S_2$. It is worth noting that the IR spectra of **5a-d** were devoid of the C-Cl bond stretching vibration in the range of 780-840 cm^{-1} which is a clear indication of its replacement with nucleophiles. In conclusion, the sequential treatment of the newly reported 5-bromo-2-chloro-4-methyl-6-(1-methylhydrazino)pyrimidine (2) with carbondisulfide and alkylhalides in basic ethanol which was followed by subsequent intramolecular heterocyclization in basic acetonitrile is a new, efficient and general access to pyrimido[4,5-*e*][1,3,4]thiadiazine derivatives.

EXPERIMENTAL

Melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu Spectrometer. The ^{1}H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. The mass spectra were scanned on a Varian Mat CH-7 instrument at 70 eV. Elemental analysis was obtained on a Thermo Finnigan Flash EA microanalyzer. The purity of all new compounds synthesized was tested by TLC using chloroform as mobile phase.

5-Bromo-2-chloro-4-methyl-6-(1-methylhydrazino)pyrimidine (2). A solution of 5-bromo-2,4-dichloro-6-methylpyrimidine (2.42 g, 10 mmoles) and triethylamine (1.01 g, 10 mmoles) in chloroform (20 ml), was added at once to a solution of methylhydrazine (0.46 g, 10 mmoles) in chloroform (10 ml). The resulting solution was stirred for 15 minutes at room temperature. The solvent was removed under reduced pressure and the residue was washed with water and recrystallized from ethanol as an orange powder in 80% yield, mp 99-101°C, IR: 840, 2900, 2960, 3280, 3360 cm^{-1}, ^{1}HNMR: ($CDCl_3$) δ, 2.52 (s, 3H, CH_3), 3.38 (s, 3H, N- CH_3), 4.2 (s, 2H, NH_2); ms:m/z, 250 (58%), 252 (75%), 254 (19%), 234 (100%).

General procedure for preparation of 3-alkylthio-7-chloro-1,5-dimethyl- pyrimido[4,5-*e*] 1,3,4 thiadiazines. A solution of 1-(5-bromo-2-chloro-6-methylpyrimidin-4-yl)-1-methylhydrazine (2.51 g, 10 mmoles), triethylamine (1.01 g, 10 mmoles), carbondisufide (0.76 g, 10 mmoles) and alkylhalide (iodomethane, bromoethane, 1-bromopropane, 1-bromobutane or benzylchloride) (10 mmoles) in ethanol (20 ml) was stirred for 12 hours. Then the solvent was removed under reduced pressure, the residue was dissolved in 20 ml of acetonitril, triethylamine (1.01 g, 10mmoles) was added and the resulting solution was refluxed under nitrogen atmosphere for 4 hours. The solvent was evaporated and the residue was purified by column chromatography over silica gel eluted with chloroform: hexane (1: 1) to give products **4a-e**.

7-Chloro-1,5-dimethyl-3-(methylsulfanyl)-1*H*-pyrimido-[4,5-*e*][1,3,4]thiadiazine (4a) was obtained as a green powder in 35% yield, mp 90-92 °C, IR: 800, 2900, 2940 cm^{-1} ; ^{1}HNMR: ($CDCl_3$) δ, 2.2 (s, 3H, 5-CH_3), 2.41 (s, 3H, S-CH_3), 3.34 (s, 3H, 1-CH_3); ms: m/z, 260 (60), 262 (20), 184 (100%). *Anal.* Calcd. for $C_8H_9ClN_4S_2$: C, 36.85; H, 3.48; N, 21.49; S, 24.59. Found: C, 36.73; H, 3.44; N, 21.35; S,24.38.

7-Chloro-3-(ethylsulfanyl)-1,5-dimethyl-1*H*-pyrimido[4,5-*e*]-[1,3,4]thiadiazine (4b) was obtained as a green powder in 30% yield, mp 50 °C, IR: 820, 2900, 2950 cm^{-1}; ^{1}HNMR: ($CDCl_3$) δ, 1.35(t, 3H,CH_3),2.2 (s, 3H, 5-CH_3), 3.05 (q, 2H, S-CH_2), 3.4 (s, 3H, 1-CH_3); ms: m/z, 274 (79), 276 (25), 184 (100%). *Anal.* Calcd. for $C_9H_{11}ClN_4S_2$: C, 39.34; H, 4.03; N, 20.39; S, 23.34. Found: C, 39.50; H, 4.1; N, 20.25; S,23.20.

7-Chloro-1,5-dimethyl-3-(propylsulfanyl)-1*H*-pyrimido-[4,5-*e*][1,3,4]thiadiazine (4c) was obtained as a green powder in 36% yield, mp 43-45 °C, IR: 840, 2880, 2920 cm^{-1}; ^{1}HNMR: ($CDCl_3$) δ, 1.03 (t, 3H,CH_3), 1.6 (sextet, 2H,CH_2), 2.2 (s, 3H, 5-CH_3), 3.01(t, 2H,S-CH_2), 3.32 (s, 3H, 1-CH_3); ms: m/z, 288 (70), 290 (23), 184 (100). *Anal.* Calcd. for $C_{10}H_{13}ClN_4S_2$: C, 41.59; H, 4.54; N, 19.40; S, 22.20. Found : C, 41.42; H, 4.38; N, 19.51; S,22.10.

3-(Butylsulfanyl)-7-chloro-1,5-dimethyl-1*H*-pyrimido[4,5-*e*]-[1,3,4]thiadiazine (4d) was obtained as a green powder in 30% yield, mp 45-47 °C, IR: 800, 2900, 2950 cm^{-1}; ^{1}HNMR: ($CDCl_3$) δ,0.95 (t, 3H,CH_3), 1.2-1.7 (multiplet, 4H, 2CH_2), 2.25 (s, 3H, 5-CH_3), 3.05 (t, 2H, S-CH_2), 3.4 (s, 3H, 1-CH_3); ms: m/z, 302 (50), 304 (17), 184 (100). *Anal.* Calcd. for $C_{11}H_{15}ClN_4S_2$: C, 43.63; H, 4.99; N, 18.50; S, 21.18. Found : C, 43.71; H, 4.85; N, 18.59; S, 21.03.

3-(Benzylsulfanyl)-7-chloro-1,5-dimethyl-1*H*-pyrimido-[4,5-*e*][1,3,4]thiadiazine (4e) was obtained as a green powder in 35% yield, mp 97-99 °C, IR: 780, 2910, 2960 cm^{-1}; ^{1}HNMR: ($CDCl_3$) δ, 2.25 (s, 3H, 5-CH_3), 3.4 (s, 3H, 1-CH_3), 4.25 (t, 2H, S-CH_2), 7.4 (multiplet,5H),; ms: m/z, 336 (46), 338 (15), 299 (100). *Anal.* Calcd. for $C_{14}H_{13}ClN_4S_2$: C, 49.92; H, 3.89; N, 16.63; S, 19.04. Found : C, 50.05; H, 3.95; N, 16.55; S,18.93.

General procedure for the reaction of 3-alkylthio-7-chloro-1,5-dimethylpyrimido[4,5-*e*][1,3,4]thiadiazines with morpholine or pyrrolidine. 3-Alkylthio-7-chloro-1,5-dimethyl-pyrimido[4,5-*e*][1,3,4]thiadiazines 4b-c,e (2 mmoles) in ethanol (10 ml) was heated under reflux with either morpholine (2.0 g)

or pyrrolidine (1.8 g) for 4 hours. The solvent was removed and the residue was washed with water and then recrystallized from ethanol to give products **5a-d**.

4-[3-(Ethylsulfanyl)-1,5-dimethyl-1*H*-pyrimido[4,5-*e*]-[1,3,4]thiadiazin-7-yl]morpholine (5a) was obtained as a green powder in 85% yield, mp 81-83 °C, IR: 2880, 2930 cm-^{1}; ^{1}HNMR: ($CDCl_3$) δ, 1.35(t, 3H,CH_3), 2.1(s, 3H, 5-CH_3), 2.9(q, 2H, S-CH_2), 3.3(s, 3H, 1-CH_3), 3.65(m, 8H, CH_2-(O&N)); ms: m/z, 325. *Anal*. Calcd. for $C_{13}H_{19}N_5OS_2$: C, 47.98; H, 5.88; N, 21.52; S, 19.70. Found : C, 48.1; H, 5.79; N, 21.45; S,19.61.

4-[1,5-Dimethyl-3-(propylsulfanyl)-1*H*-pyrimido[4,5-*e*]-[1,3,4]thiadiazin-7-yl]morpholine (5b) was obtained as a green powder in 70% yield, mp 79°C, IR: 2910, 2940 cm-^{1}; ^{1}HNMR: ($CDCl_3$) δ, 0.98(t, 3H,CH_3), 1.6(sextet, 2H,CH_2), 2.1(s, 3H, 5-CH_3), 2.9(t, 2H,S-CH_2), 3.29 (s, 3H, 1-CH_3), 3.65(m, 8H, CH_2-(O&N)); ms: m/z, 339. *Anal*. Calcd. for $C_{14}H_{21}N_5OS_2$: C, 49.53; H, 6.24; N, 20.63; S, 18.89. Found : C, 49.61; H, 6.30; N, 20.55; S,18.75

4-[3-(Benzylsulfanyl)-1,5-dimethyl-1*H*-pyrimido[4,5-*e*][1,3,4]-thiadiazin-7-yl]morpholine (5c) was obtained as a green powder in 80% yield, mp 134-136 °C, IR: 2890, 2930 cm-^{1}; ^{1}HNMR: ($CDCl_3$) δ, 2.16 (s, 3H, 5-CH_3), 3.39 (s, 3H, 1-CH_3), 3.73 (m, 8H, CH_2-(O&N)), 4.23 (s, 2H, S-CH_2), 7.4 (multiplet,5H),; ms: m/z, 387. *Anal*. Calcd. for $C_{18}H_{21}N_5OS_2$: C, 55.79; H, 5.46; N, 18.07; S, 16.55. Found : C, 55.68; H, 5.40; N, 18.20; S,16.41.

3-(Benzylsulfanyl)-1,5-dimethyl-7-tetrahydro-1*H*-1-pyrrolyl-1*H*-pyrimido[4,5-*e*][1,3,4]thiadiazine (5d) was obtained as a green powder in 70% yield, mp 101-103 °C, IR: 2900, 2940 cm-^{1}; ^{1}HNMR: ($CDCl_3$) δ, 1.93(t, 4H, 2 ((CH_2)-CH_2N),2.17 (s, 3H, 5-CH_3), 3.40 (s, 3H, 1-CH_3), 3.51(t,4H, 2(CH_2N)), 4.23 (S, 2H, S-CH_2), 7.4 (multiplet,5H); ms: m/z, 371. *Anal*. Calcd. for $C_{18}H_{21}N_5S_2$: C, 58.19; H, 5.70; N, 18.85; S, 17.26. Found: C, 58.28; H, 5.75; N, 18.81; S,17.2.

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