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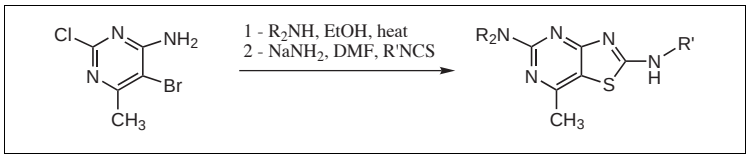

4-Amino-5-bromo-2-substituted-aminopyrimidines are readily obtained from the newly prepared 5-bromo-2,4-dichloro-6-methylpyrimidine by sequential treatment with ethanolic ammonia and secondary amines. These compounds were successfully reacted with various isothiocyanates in the presence of sodamide in DMF to form the new thiazolo[4,5-*d*] pyrimidine derivatives .

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Introduction.

The growing pharmaceutical and agrochemical interest for fused pyrimidines has focused the attention of organic chemists to search for efficient and general routes to these molecules in synthetically useful yields.

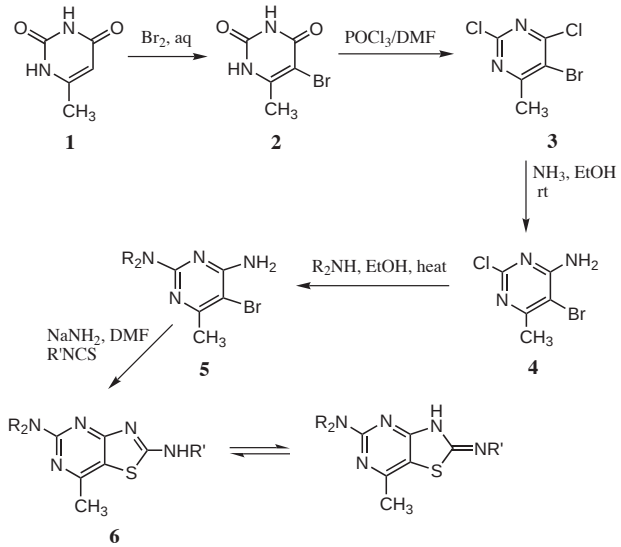
Thiazolo[4,5-*d*] pyrimidines are a class of fused heterocycles which have been described as being antiviral [1-7], antifungal [8], nucleoside analogues [9], agro-chemicals [10] and enzyme inhibitors [11] agents. Despite their importance from pharmacological and synthetic point of views, comparatively few methods for their preparation have been reported.

Molina's group described the thermal electrocyclic ring closure of certain carbodiimides and cyclocondensation of iminophosphoranes with carbon disulfide at room temperature as the only useful methods for the preparation of thiazolo[4,5-*d*]pyrimidines [12]. Other methods mainly involve heterocyclization of suitably substituted thiazoles with carbon disulfide [13], acetic anhydride/trimethy orthoformate [14,15], and guanidine [16]. The syntheses from pyrimidines are limited and mostly reported in patent literature [11,17].

Prompted by these findings and due to our ongoing studies directed towards the synthesis of fused heterocycles of biological significance [18], we became interested in developing an efficient and general route to derivatives of thiazolo[4,5-*d*] pyrimidines.

Our synthesis started from 6-methy-pyrimidin-2,4(1*H*, 3*H*)-dione **1** which was converted to the new key intermediate, 5-bromo-6-methy- pyrimidin-2,4(1*H*,3*H*)-dione **2**, by treatment with aqueous bromine at room temperature. The subsequent chlorination of this compound with phosphorus oxychloride in the presence of DMF afforded the polyhalogenated derivative **3**. The structure of products **2** and **3** was adequately supported by mass

Scheme I



spectral and microanalytical data. Selective displacement of the 4-chlorine atom with ammonia occurred at room temperature followed by subsequent displacement of the 2-chlorine atom with secondary amines in ethanol at reflux temperature to furnish the corresponding diaminopyrimidines **5a-b**. Treatment of these compounds with sodamide in DMF which was followed by heterocyclizsation with isothiocyanates furnished a host of thiazolo[4,5-*d*] pyrimidines **6 a-f** in moderate to high yields .

The structural assignments of compounds **6a-f** are based upon spectral and microanalytical data. The IR spectra did not exhibit the stretching vibration bands at 3450 and 3300 cm^{-1} (broad, NH_2) due to precursors but showed a sharp band at 3380 cm^{-1} for the NH absorption.

Further proof came from the ^1H NMR spectra, which showed the disappearance of a broad 2H signal belonging to NH_2 moiety of compounds **5a-b** and the appearance of two sharp 1H (NH) signals with different chemical shifts indicating the construction of a thiazole ring around the pyrimidine nucleous.

It is notworthy that the presence of these two NH signals clearly demonstrate the tautomeric equilibrium which exists between amine and iminie forms of the thiazolo[4,5-*d*] pyrimidines. The ratio between these two tautomers is nearly 1: 1.

In conclusion, the sequential treatment of the newly prepared 5-bromo-2,4-dichloro-6-methylpyrimidine with ethanolic ammonia and secondary amines which was followed by interaction with sodamide in DMF and subsequent heterocyclization with isothiocyanates is a new, efficient and general access to thiazolo[4,5-*d*]-pyrimidine derivatives.

EXPERIMENTAL

The melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu Spectrometer. The ^{13}C NMR spectra were recorded on a Bruker BRX 500 AVANCE spectrometer. The ^1HNMR (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.

5-Bromo-6-methyl-pyrimidine-2,4(1*H*,3*H*)-dione (**2**).

To a suspension of 6-methyl-pyrimidine-2,4(1*H*,3*H*)-dione (2.52 g, 20 mmoles) in water (40 mL), bromine (3.2 g, 20 mmoles) was added dropwise with vigorous stirring over a period of 1 minute. Stirring was continued for further 30 minutes. The mixture was heated to boil and then cooled to room temperature to give a white residue which was collected by filtration, washed with warm water and dried at 80 °C (3.28 g, 80% yield, mp 260 °C (dec). IR: 3200 cm^{-1} (NH), 1550 cm^{-1} (C=O) ; ^1H NMR (d_6-DMSO): δ, 2.13 (s, 3H,CH_3),11.24 (s, 1H, N_1H), 11.37 (s, 1H, N_3H); ^{13}C NMR (d_6-DMSO): δ, 19.52, 95.05, 150.27, 151.38, 160; ms: m/z, 204 (90%), 206 (90%).

5-Bromo-2,4-dichloro-6-methylpyrimidine (**3**).

A mixture of 5-bromo-6-methyl-pyrimidine-2,4(1*H*,3*H*)-dione **2** (2.05 g, 10 mmoles) and dimethylformamide (0.5 mL) in phosphoroxychloride (10 mL) was heated under reflux for 3 hours. The solvent was removed *in vacuo* and the residue was added to ice. The precipitate was collected by filtration and crystallized from petroleum ether (40-60 °C) as pale green crystals (2.06 g, 85% yield, mp 44-46 °C); ^1H NMR ($CDCl_3$): δ, 2.75 (s, 3H, CH_3); ^{13}CNMR ($CDCl_3$): δ, 25.64, 119.24, 157.64, 161.6, 171.2; ms: m/z, 240 (55%), 242 (90%), 244 (43%), 246 (6%).

Anal. Calcd. for $C_5H_3BrCl_2N_2$: C, 24.83; H, 1.25; N, 11.58. Found: C, 24.9; H, 1.23; N, 11.65.

5-Bromo-2-chloro-6-methylpyrimidin-4-amine (**4**).

A solution of 5-bromo-2,4-dichloro-6-methylpyrimidine (2.42 g, 10 mmoles) in ethanol (25 mL) and concentrated ammonia (2 mL) was stirred in a closed flask at room temperature for 12 hours. The creamy like precipitate was collected by filtration ,washed with warm water and dried at 80 °C (2.0 g, 90% yield, mp 172-174 °C); ^1H NMR ($CDCl_3$): δ, 2.51 (s, 3H, CH_3), 6.08 (s, 2H, NH_2); ^{13}CNMR ($CDCl_3$): δ, 24.25, 101.86, 157.96, 161.47, 166.5; ms: m/z, 221 (78%), 223 (100%), 225(25%).

General Procedure for the Reaction of 5-Bromo-2-chloro-6-methylpyrimidin-4-amine (**4**) with Morpholine or Pyrrolidine.

5-Bromo-2-chloro-6-methylpyrimidin-4-amine (**4**) (2.22 g, 10 mmoles) in ethanol (25 mL) was heated under reflux with either morpholine (2.0 g) or pyrrolidine (1.8 g) for 4 hours. Then water (20 mL) was added and the solution was kept over night , the precipitate was collected by filtration and washed with warm water and dried at 80 °C to give **5a** and **5b** respectively.

5-Bromo-6-methyl-2-morpholin-4-ylpyrimidin-4-amine (**5a**).

This compound was obtained as a creamy powder in 70% yield , mp 123-126 °C; IR: 3300 and 3450 cm^{-1} (NH_2) ;^1H NMR ($CDCl_3$): δ, 2.49 (s, 3H, CH_3), 3.55 (m, 8H, CH_2-(O&N)), 5.2 (s, 2H, NH_2); ^{13}CNMR ($CDCl_3$): δ, 24.42, 44.28, 48.86, 66.62, 91.39, 159.87, 164.19, 166.35; ms: m/z, 272 (90%), 274 (90%).

Anal. Calcd. for $C_9H_{13}BrN_4O$: C, 39.58; H, 4.8; N, 20.51. Found: C, 39.24; H, 4.61; N, 20.31.

5-Bromo-6-methyl-2-pyrrolidin-1-ylpyrimidin-4-amine (**5b**).

This compound was obtained as a creamy powder in 77% yield, mp 199-202 °C, IR: 3320 and 3460 cm^{-1} (NH_2) ; ^1H NMR ($CDCl_3$): δ, 1.94 (t, 4H, 2 ((CH_2)-CH_2N), 2.51 (s, 3H, CH_3), 3.5 (t, 4H, 2(CH_2N)), 5.1 (s, 2H, NH_2); ^{13}C NMR ($CDCl_3$): δ, 24.55, 25.57, 50.7, 90.6, 158.58, 159.8, 164.1; ms: m/z, 256 (80%), 258 (80%).

Anal. Calcd. for $C_9H_{13}BrN_4$: C, 42.04; H, 5.10; N, 21.79. Found: C, 42.18; H, 5.02; N, 21.89.

General Procedure for Preparation of Thiazolo[4,5-*d*]-pyrimidines.

To a solution of the foregoing compounds (**5a** and **5b**) (1 mmol) in dimethylformamide (2 mL) sodium amide (0.078 g, 2 mmoles) was added on stirring . The stirring was continued for 5 minutes, then an appropriate isothiocyanate (3 mmoles) was added. The solution was heated at 130 °C for 1 hour, then poured into a solution of water (10 mL) and acetic acid (1 mL). The mixture was extracted with chloroform (3x5mL), dried at

reduced pressure, then crystallized from absolute ethanol to give compounds **6a-f** .

N-Ethyl-7-methyl-5-morpholin-4-yl[1,3]thiazolo[4,5-*d*]pyrimidin-2-amine (**6a**).

This compound was obtained as a green powder in 56% yield, mp 170-171 °C, IR: 3380 cm^{-1} (NH); ^{1}H NMR ($CDCl_3$): δ, 1.35 (t,3H, (CH_3)-CH_2), 2.43 (s, 3H, CH_3), 3.4-3.7 (m, 10H, CH_2-(O&N&NH)), 8.50&11.09(s, 1H, two NH); ms: m/z, 279, 281.

Anal. Calcd. for $C_{12}H_{17}N_5OS$: C, 51.59; H, 6.13; N, 25.07; S, 11.48. Found : C, 51.7; H, 6.08; N, 25.1; S, 11.25.

N-Butyl-7-methyl-5-morpholin-4-yl[1,3]thiazolo[4,5-*d*]pyrimidin-2-amine (**6b**).

This compound was obtained as a green powder in 60% yield, mp 138-140, IR: 3370 cm^{-1} (NH); ^{1}H NMR ($CDCl_3$): δ, 0.95 (t,3H, (CH_3)-CH_2), 1.45-1.65 (m, 4H, (CH_2)-CH_2&(CH_2)-CH_3), 2.45 (s, 3H, CH_3), 3.6-3.8 m, 10H, CH_2-(O&N&NH)), 8.50&11.09 (s, 1H, two NH); ms: m/z, 307, 309.

Anal. Calcd. for $C_{14}H_{21}N_5OS$: C, 54.70; H, 6.89; N, 22.78; S, 10.43. Found: C, 54.82; H, 6.81; N, 22.86; S, 10.25.

7-Methyl-5-morpholin-4-yl-*N*-phenyl[1,3]thiazolo[4,5-*d*]pyrimidin-2-amine (**6c**).

This compound was obtained as a brown powder in 38% yield, mp 166-169, IR: 3390 cm^{-1} (NH); ^{1}H NMR ($CDCl_3$): δ, 2.45 (s, 3H, CH_3), 3.8 (m, 8H, CH_2-(O&N)), 7.2-7.7 (m, 5H, aromatic), 8.7&13.05 (s, 1H, two NH); ^{13}C NMR ($CDCl_3$): δ, 24.95, 44.34, 66, 91.96, 123.67, 126.24, 128.62, 137.69, 153.88, 157.16, 166.76, 178.23; ms: m/z , 327,329.

Anal. Calcd. for $C_{16}H_{17}N_5OS$: C, 58.70; H, 5.23; N, 21.39; S, 9.79. Found: C, 58.55; H, 5.15; N, 21.45; S, 9.6.

N-ethyl-7-methyl-5-pyrrolidin-1-yl[1,3]thiazolo[4,5-*d*]pyrimidin-2-amine (**6d**)

This compound was obtained as a green powder in 65% yield, mp 159-160, IR: 3380 cm^{-1} (NH); ^{1}HNMR: ($CDCl_3$) δ, 1.32 (t,3H, (CH_3)-CH_2), 2.01 (m, 4H, $2(CH_2)$-CH_2N), 2.43 (s, 3H, CH_3), 3.5 (t, 4H, $2(CH_2N)$), 3.7 (q, 2H, $(NH$-$CH_2)$-CH_3), 8.42&11.42(s, 1H, two NH); ms: m/z , 263, 265.

Anal. Calcd. for $C_{12}H_{17}N_5S$: C, 54.73; H, 6.51; N, 26.59; S, 12.18 Found : C, 54.6; H, 6.55; N, 26.65; S, 12.02.

N-buthyl-7-methyl-5-pyrrolidin-1-yl[1,3]thiazolo[4,5-*d*]pyrimidin-2-amine (**6e**)

This compound was obtained as a green powder in 58% yield, mp 151-154, IR: 3370 cm^{-1} (NH); ^{1}HNMR: ($CDCl_3$) δ, 0.95 (t,3H, (CH_3)-CH_2), 1.3-1.7 (m, 4H, (CH_2)-CH_2&(CH_2)-CH_3), 2.01 (m, 4H, $2(CH_2)$-CH_2N), 2.42 (s, 3H, CH_3), 3.5 (t, 4H,$2(CH_2N)$), 3.7 (q, 2H, $(NH$-$CH_2)$-CH_3), 8.45&11.4(s, 1H, two NH); ^{13}CNMR: ($CDCl_3$) δ, 13.63, 20.2, 25.22, 25.36, 30.67, 45.76, 46.76, 90.68, 154.17, 156.2, 166.5, 179.73; ms: m/z, 291,293.

Anal. Calcd. for $C_{14}H_{21}N_5S$: C, 57.70; H, 7.26; N, 24.03; S, 11.00 Found : C, 57.76; H, 7.2; N, 24.11; S, 10.81.

7-Methyl-N-phenyl-5-pyrrolidin-1-yl[1,3]thiazolo[4,5-*d*]pyrimidin-2-amine(**6f**)

This compound was obtained as a brown powder in 40% yield, mp 150-153, IR: 3380 cm^{-1} (NH).; ^{1}HNMR: ($CDCl_3$) δ, 1.95 (m, 4H, $2(CH_2)$-CH_2N), 2.41 (s, 3H, CH_3), 3.5 (t, 4H, $2(CH_2N)$), 7.2-7.6 (m, 5H, aromatic), 8.6&13.36 (s, 1H, two NH); ms: m/z , 311, 313.

Anal. Calcd. for $C_{16}H_{17}N_5S$: C, 61.71; H, 5.50; N, 22.49; S, 10.30 Found : C, 61.6; H, 5.54; N, 22.55; S, 10.12.

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