

Novel synthesis of Pyrimido[4,5-*e*] [1,3,4] thiadiazines

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Abstract – Treatment of 1-(5-bromo-2-chloro-6-methylpyrimidin-4-yl)-1-methylhydrazine with dimethylthiocarbamoylchloride gave 7-chloro-*N,N*,1,5-tetramethyl-1H-pyrimido[4,5-*e*][1,3,4]thiadiazin-3-amine in basic acetonitrile. The latter compounds were reacted with secondary amines in boiling ethanol to afford the related 7-amino derivatives.

Keywords: 1-(5-bromo-2-chloro-6-methylpyrimidin-4-yl)-1-methylhydrazine, dimethylthiocarbamoylchloride, pyrimidothiadiazine, 15- lipoxygenase.

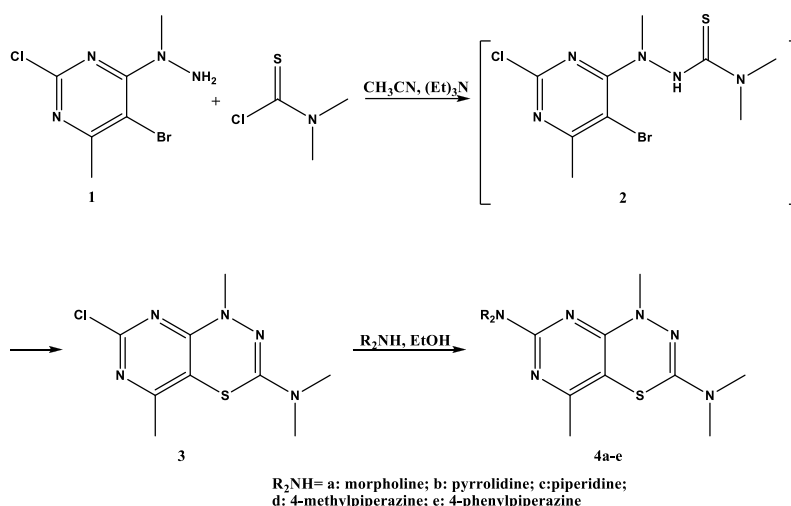
INTRODUCTION

Our motives in pyrimido[4,5-*e*] [1,3,4] thiadiazine synthesis emerges from few reports on their variety biological applications. These compounds have been described as being nucleoside analogues [1,2], antiinflammatory, hypotensive, diuretic [3,4], and phosphodiesterase inhibitor [4] agents. Despite their importance from pharmacological and synthetic point of views, comparatively few methods for their preparation have been reported. This report and pursuing of our research on biologically active compounds [5-8], convinced us to prepare a novel group of this class of heterocycles.

RESULTS AND DISCUSSION

The current synthesis is based upon intramolecular heterocyclization of the key intermediate hydrazinecarbothioamide **2** which was *in situ* prepared from the reaction of 1-(5-bromo-2-chloro-6-methylpyrimidin-4-yl)-1-methylhydrazine **1** with dimethylthiocarbamoylchloride as shown in **Scheme 1**.

In the second stage 7-chloro-*N,N*,1,5-tetramethyl-1H-pyrimido[4,5-*e*][1,3,4]thiadiazin-3-amine **3** was reacted with secondary amines in boiling ethanol to afford the new pyrimido[4,5-*e*][1,3,4]thiadiazine derivatives **4a-e**.



Scheme 1: preparation of compounds **3** and **4a-e**.

The structure of new derivatives **3** and **4a-e** were confirmed by their spectral and microanalytical data. The IR spectrum of **3** was devoid of the stretching vibration bands at 3450 & 3300 cm^{-1} due to NH_2 functionality of the precursor **1** or intermediate **2**. The ^1H NMR spectrum of **3** was also devoid of the broad NH_2 signal at δ 4.2 ppm of the precursor but showed two singlets at δ 3.11 & 3.17 ppm assignable to 6 protons for $\text{N}(\text{Me})_2$ group which indicates the formation of compound **3**. The molecular ions of **3** ($M: M+2$) was observed at 257 & 259 (60%:20%) corresponding to the molecular formula $\text{C}_9\text{H}_{12}\text{ClN}_5\text{S}$, which was adequately confirmed by its elemental analysis (C, 42.16; H, 4.78; N, 26.96; S, 12.21).

The IR spectra of compounds **4a-e** did not show the stretching vibration band of C-Cl of the precursor **3** and verified the replacement of chlorine atom by amines, which was amplified by lacking of the expected isotopic pattern of chlorine atom in their mass spectra. The ^1H NMR spectra of **4a-e** also showed the methylene groups due the substituted amines plus a slight shift of methyl groups of their precursor **3** to high field.

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 ^1H 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. 1-(5-Bromo-2-chloro-6-methylpyrimidin-4-yl)-1-methylhydrazine **1** and its precursor were prepared according to published method [9,10].

7-Chloro-*N,N*,1,5-tetramethyl-1*H*-pyrimido[4,5-*e*][1,3,4] thiadiazin-3-amine (**3**)

1-(5-Bromo-2-chloro-6-methylpyrimidin-4-yl)-1-methylhydrazine **1** (2.5 gr, 10 mmol), dimethylthiocarbamoylchloride (1.23 gr, 10mmol) and triethylamine (3ml) were dissolved in acetonitrile (20ml) and boiled under reflux condition for 3 hr. The solvent was removed under *vacuu* and the residue was recrystallized from hexane to obtaine yellow powder in 70% yield. mp 47-49 °C; IR: 800, 2900, 2950 cm⁻¹; ¹HNMR: (CDCl₃) δ, 2.25 (s, 3H, 5-CH₃), 3.11 & 3.17 (s, 6h, N(Me)₂), 3.4 (s, 3H, 1-CH₃); ms: m/z , 257 (60), 259 (20). *Anal.* Calcd. for C₉H₁₂ClN₅S: C, 41.94; H, 4.69; N, 27.17; S, 12.44 Found : C, 42.16; H, 4.78; N, 26.96; S, 12.21.

General procedure for the reaction of 7-Chloro-*N,N*,1,5-tetramethyl-1H-pyrimido[4,5-*e*][1,3,4]thiadiazin-3-amine (**3**) with amines

7-Chloro-*N,N*,1,5-tetramethyl-1H-pyrimido[4,5-*e*] [1,3,4]thiadiazin-3-amine **3** (2 mmol) in ethanol (10ml) was heated under reflux with 1ml of either morpholine, pyrrolidine, piperidine, 1-methylpiperazine or 1-phenylpiperazine for 4 hr. The solvent was removed under *vacuu* and the residue was recrystallized from ethanole to obtaine compounds **4a-e**.

N,N,1,5-Tetramethyl-7-(morpholin-4-yl)-1H-pyrimido[4,5-*e*][1,3,4]thiadiazin-3-amine (**4a**)

This compound was obtained as a green powder in 60% yield, mp 77-78 °C; IR: 2890, 2930 cm⁻¹; ¹HNMR: (CDCl₃) δ, 2.16 (s, 3H, 5-CH₃), 3.02 & 3.08 (s, 6h, N(Me)₂), 3.35 (s, 3H, 1-CH₃), 3.73 (m, 8H, CH₂-(O&N)); ms: m/z , 308. *Anal.* Calcd. for C₁₃H₂₀N₆OS: C, 50.63; H, 6.54; N, 27.25; S, 10.40 Found : C, 50.91; H, 6.78; N, 27.07; S, 10.18.

N,N,1,5-Tetramethyl-7-(pyrrolidin-1-yl)-1H-pyrimido [4,5-*e*][1,3,4]thiadiazin-3-amine (**4b**)

This compound was obtained as a green powder in 70% yield, mp 72-74 °C; IR: 2900, 2930 cm⁻¹; ¹HNMR: (CDCl₃) δ, 1.93(t, 4H, 2 ((CH₂)-CH₂N), 2.15 (s, 3H, 5-CH₃), 3.03 & 3.10 (s, 6h, N(Me)₂), 3.37 (s, 3H, 1-CH₃), 3.55 (t, 4H, 2(CH₂N)); ms: m/z , 292. *Anal.* Calcd. for C₁₃H₂₀N₆S: C, 53.40; H, 6.89; N, 28.74; S, 10.97 Found : C, 53.61; H, 6.97; N, 28.57; S, 10.71.

N,N,1,5-Tetramethyl-7-(piperidin-1-yl)-1H-pyrimido [4,5-*e*][1,3,4]thiadiazin-3-amine (**4c**)

This compound was obtained as a green powder in 75% yield, mp 83-85 °C; IR: 2870, 2910 cm⁻¹; ¹HNMR: (CDCl₃) δ, 1.2-1.7 (m, 6H, 3CH₂), 2.17 (s, 3H, 5-CH₃), 3.04 & 3.11 (s, 6h, N(Me)₂), 3.32 (s, 3H, 1-CH₃), 3.52 (t, 4H, 2(CH₂N)); ms: m/z , 306. *Anal.* Calcd. for C₁₄H₂₂N₆S: C, 54.87; H, 7.24; N, 27.43; S, 10.46 Found : C, 55.09; H, 7.38; N, 27.25; S, 10.21.

N,N,1,5-Tetramethyl-7-(4-methylpiperazin-1-yl)-1H-pyrimido[4,5-*e*][1,3,4]thiadiazin-3-amine (**4d**)

This compound was obtained as a green powder in 55% yield, mp 65-67 °C; IR: 2850, 2920 cm⁻¹; ¹HNMR: (CDCl₃) δ, 2.15 (s, 3H, 5-CH₃), 2.30 (m, 7H, 2(CH₂N)-CH₃), 3.04 & 3.10 (s, 6h, N(Me)₂), 3.34 (s, 3H, 1-CH₃), 3.49 (t, 4H, 2(CH₂N)); ms: m/z , 321. *Anal.* Calcd. for C₁₄H₂₂N₆S: C, 52.31; H, 7.21; N, 30.50; S, 9.98 Found : C, 52.55; H, 7.39; N, 30.28; S, 9.71.

N,N,1,5-Tetramethyl-7-(4-phenylpiperazin-1-yl)-1*H*-pyrimido[4,5-*e*][1,3,4]thiadiazin-3-amine (**4d**)

This compound was obtained as a green powder in 80% yield, mp 92-94 °C; IR: 2870, 2940 cm⁻¹; ¹HNMR: (CDCl₃) δ, 2.17 (s, 3H, 5-CH₃), 2.37 (t, 4H, 2(CH₂N)-Ph), 3.03 & 3.09 (s, 6h, N(Me)₂), 3.35 (s, 3H, 1-CH₃), 3.52 (t, 4H, 2(CH₂N)), 7.2-7.5 (m, 5H, aromatic); ms: m/z, 383. *Anal.* Calcd. for C₁₉H₂₅N₇S: C, 59.50; H, 6.57; N, 25.57; S, 8.36 Found : C, 59.75; H, 6.71; N, 25.32; S, 8.12.

CONCLUSION

In conclusion sequential treatment of 1-(5-bromo-2-chloro-6-methylpyrimidin-4-yl)-1-methylhydrazine with dimethylthiocarbamoylchloride and amines is a general and convenient access to novel pyrimido[4,5-*e*] [1,3,4] thiadiazines.

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