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Convenient Synthesis of Novel Pyrimido[4, 5- *b*][1, 5]benzothiazepines

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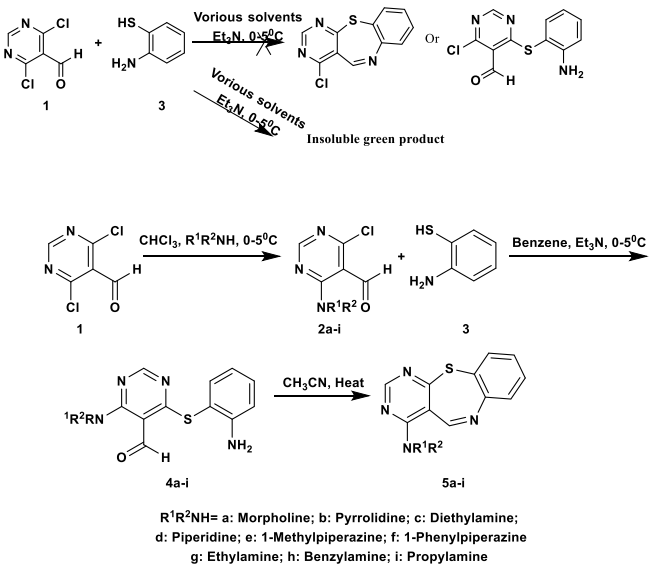
Abstract: Reaction of 4,6-Dichloropyrimidine-5-carbaldehyde with amines in chloroform gave 4-(substitutedamino)-6-chloro-pyrimidine-5-carbaldehydes derivatives at low temperature. Treatment of the latter products with 2-aminobenzenethiol in alkaline benzene and then in boiling acetonitrile gave a novel group of 11H-pyrimido[4,5-b][1, 5]benzodiazepine derivatives. Structures of the products confirmed by ^{1}HNMR, IR and Mass spetra.

Introduction

The growing pharmaceutical and agrochemical interest for fused pyrimidines has focused the attention of researchers to search for efficient and general routes to these molecules in synthetically useful yields. Among the privileged heterocyclic scaffolds, [1,5]benzothiazepines and fused [1,5]benzothiazepines were on the scope of chemists efforts for several years[1,2]. These compounds have been described as Calcium channel blockers[3-6], hypotensive[7-10], drugs of liver diseases[11,12], antidepressants[13-15], anticholinesterase inhibitors[16-17], anticancer[18-23], diuretics [24], antimicrobials[25-38], anti HIV[39-41] and anti tuberculosis[42,43] agents. The useful procedures for the preparation of 1,5-benzothiazepines are mainly based on the condensation of 2-aminobenzenethiol with α, β- unsaturated ketones[2]. These findings encouraged scientists to prepare pyrimido[4,5-*b*][1,4]benzothiazepines by a) condensation of 5-aminopyrimidine-4-thiol with 2-chlromethylbenzoates[44] and b) 4-chloropyrimidin-5-amine on the Bischler−Napieralski-type reactions[45] as a potential biologically active scaffold. Prompt by these findings and in continuation of our studies on the synthesis of N, S containing heterocycles[46-53] we decided to prepare a group of pyrimido[4,5-b][1,5]benzothiazepine derivatives, which have been largely overlooked as a class of pyrimidobenzothiazepine.

Results and Discussion

Our first attemt for the preparation of pyrimido[4,5- *b*][1, 5]benzodiazepine was the condensation of 4,6-dichloropyrimidine-5-carbaldehyde **1**[54] with 2-aminobenzenethiol **3**, which achieved an insoluble green product even in various temperatures. It seems that both SH and NH_2 moieties of 2- aminobenzenethiol **3**, replaced over the number 4 position of two 4,6-dichloropyrimidine-5-carbaldehyde **1** molecules to give a polymeric product as shown in ***Scheme 1***. For fixing of this problem, it was decided to substitute a chlorine atom of 4,6-dichloropyrimidine-5-carbaldehyde **1** by amines. So 4,6-dichloropyrimidine-5-carbaldehyde **1** reacted with amines according to an earlier report[55] as shown in ***Scheme 1*** and the strategy for the synthesis of pyrimido[4,5-*b*][1,5]benzothiazepines **5a-i** based on the condensation of 2-aminobenzenethiol **3** with 4-(substitutedamino)-6-chloro-pyrimidine-5-carbaldehydes **2a-i.**



Scheme 1. General rout for the preparation of pyrimido[4,5-*b*][1,5]benzothiazepine derivatives.

Displacement of the 6- chlorine atom of **2a-i** with 2-aminobenzenethiol **3** occurred at 0-5^{0}C temperature in benzene to give products **4a-i**. The products of this reaction concentrated and then underwent an intramolecular cyclization in boiling acetonitrile without further purification to give final products. The remaining benzene in the concentrated products **4a-i** plays an important role on the removal of the produced water during the cyclization reaction in acetonitrile. The structural assignment of compounds **5a-i** based upon the spectral and microanalytical data. The IR spectra did not exhibit the stretching vibration bands at 3450&3300 cm^{-1} (broad, NH_2) or 1660cm^{-1} (sharp, C=O) due to precursors but showed a sharp band at 1570 cm^{-1} for C=N absorption belonging to products. Further proof came from the ^{1}H NMR spectra, which showed the disappearance of a sharp 1H signal at δ, 10.2 ppm belonging to CHO moiety of precursors **2a-i** and the appearance of a new sharp 1H signal at δ, 7.5 ppm assignable to C_5H of products **5a-i** indicating the construction of a [1,5]benzothiazine ring around the pyrimidine nucleus. More proof came from mass spectra, which verified the

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disappearance of isotopic effect of Chlorine atom of precursor's **2a-i** but showed a negligible isotopic effect due to Sulfur atom of products **5a-i**. Elemental analysis of the products **5a-i** showed no significant difference with the calculated values.

Conclusions

In conclusion, treatment of 4-(substitutedamino)-6-chloro-pyrimidine-5-carbaldehydes with 2-aminobenzenethiol in benzene and then in boiling acetonitril is an efficient route to pyrimido[4,5-*b*][1,5]benzothiazepin ederivatives.

Experimental Section

IR spectra obtained on a 4300 Shimadzu spectrometer in KBr pellets. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra of products were carried out on Bruker Avance spectrometer in Chloroform-d ($CDCl_3$) with tetramethylsilane (TMS) as an internal standard. Electron ionization mass spectra obtained on a Varian Mat CH-7 instrument at 70 eV. Elemental analysis obtained on a Thermo Finnigan Flash EA microanalyzer. Melting points were determined on an Electrothermal 9100 apparatus.

4-(Substitutedamino)- pyrimido[4, 5- *b*][1, 5]benzothiazepine 5a-i (General method).

2-Aminobenzenethiol (1.25gr, 10mmol) added to a solution of each compounds **2a-i** (10mmol) and triethylamine (1.01gr, 10mmol) in benzene (100ml) in 0–5°C and stirred for 4 hours. The reaction`s volume decreased under reduced pressure to around 30ml and then dissolved in acetonitrile (70ml) and refluxed for 8 hours. Solvent removed under reduced pressure and the residue purified by twice crystallization from ethanol to obtain products **5a-i**.

4-(Morpholin-4-yl)pyrimido[4, 5- *b*][1, 5]benzothiazepine 5a

Yield 1.73 g (58%), green powder, mp 137.5–139°C. IR spectrum, v, cm–1: 1570 (C=N); 2960, 2900 (CH_2).

^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.52 (4H, t, *J* = 16.1, $(CH_2)_2$N); 3.70 (4H, t, *J* = 16.1, $(CH_2)_2$O); 7.05-7.20 (4H, m, C_7H-C_{10}H); 7.56 (1H, s, C_5H); 8.44 (1H, s, C_2H). ^{13}C NMR spectrum, δ, ppm: 52.5 ($(CH_2)_2$N); 66.7 $(CH_2)_2$O); 104.6 (C_4-**C**-C_5); 123.0 (C_7); 127.0 (C_8); 128.1 (C_9); 131.1 (C_{10}); 136.0 (S-**C**-C_{10}); 154.1 (N_6-**C**-C_7); 159.0 (C_2); 161.1 (C_5); 169.0 (C_4); 189.5 (N_1-**C**-S_{10}). Mass spectrum, *m*/*z* (*I*rel, %): 298 [M]+ (31), 28 $[CH_2CH_2]^{+\cdot}$ (100). *Anal*. Calcd. For $C_{15}H_{14}N_4OS$: C, 60.38; H, 4.73; N, 18.78; S, 10.75 Found: C, 60.59; H, 4.79; N, 18.72; S, 10.52.

4-(Pyrrolidin-1-yl)pyrimido[4, 5- *b*][1, 5]benzothiazepine 5b

Yield 1.80 g (64%), green powder, mp 163.5–164°C. IR spectrum, v, cm–1: 1570 (C=N); 2960, 2900 (CH_2).

^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.53 (4H, t, *J* = 16.1, $(\mathbf{CH_2}CH_2)_2$N); 3.51 (4H, t, *J* = 16.1, $(CH_2\mathbf{CH_2})_2$N); 7.05-7.20 (4H, m, C_7H-C_{10}H); 7.56 (1H, s, C_5H); 8.44 (1H, s, C_2H). ^{13}C NMR spectrum, δ, ppm: 25.5 ($(\mathbf{CH_2}CH_2)_2$N); 52.1 ($(\mathbf{CH_2}CH_2)_2$N); 104.6 (C_4-**C**-C_5); 123.0 (C_7); 127.1 (C_8); 128.1 (C_9); 131.0 (C_{10}); 136.0 (S-**C**-C_{10}); 154.1 (N_6-**C**-C_7); 159.1 (C_2); 161.0 (C_5); 169.1 (C_4); 189.5 (N_1-**C**-S_{10}). Mass spectrum, *m*/*z* (*I*rel, %): 282 [M]+ (20), 28 $[CH_2CH_2]^{+\cdot}$ (100).

Anal. Calcd. For $C_{15}H_{14}N_4S$: C, 63.80; H, 5.00; N, 19.84; S, 11.36 Found: C, 63.71; H, 4.96; N, 19.73; S, 11.18.

***N*,*N*-Diethylpyrimido[4, 5- *b*][1, 5]benzothiazepin-4-amine 5c**

Yield 1.80 g (64%), green powder, mp 181.5–183°C. IR spectrum, v, cm^{-1}: 1570 (C=N); 2960, 2900 (CH_2, CH_3).

^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.01 (6H, t, *J* = 19.0, $(\mathbf{CH_3}CH_2)_2$N); 3.21 (4H, q, *J* = 19.0, $(CH_3\mathbf{CH_2})_2$N); 7.05-7.20 (4H, m, C_7H-C_{10}H); 7.55 (1H, s, C_5H); 8.45 (1H, s, C_2H). ^{13}C NMR spectrum, δ, ppm: 13.1 ($(\mathbf{CH_3}CH_2)_2$N); 45.1 ($(CH_3\mathbf{CH_2})_2$N); 104.6 (C_4-**C**-C_5); 123.1 (C_7); 127.0 (C_8); 128.0 (C_9); 131.0 (C_{10}); 136.1 (S-**C**-C_{10}); 154.1 (N_6-**C**-C_7); 159.1 (C_2); 161.0 (C_5); 169.1 (C_4); 189.5 (N_1-**C**-S_{10}). Mass spectrum, *m*/*z* (*I*rel, %): 284 [M]+ (22), 28 $[CH_2CH_2]^{+\cdot}$ (100). *Anal*. Calcd. For $C_{15}H_{16}N_4S$: C, 63.35; H, 5.67; N, 19.70; S, 11.28 Found: C, 63.22; H, 5.61; N, 19.58; S, 11.15.

4-(Piperidin-1-yl)pyrimido[4, 5- *b*][1, 5]benzothiazepine 5d

Yield 1.92 g (65%), green powder, mp 141–143°C. IR spectrum, v, cm–1: 1570 (C=N); 2960, 2900 (CH_2).

^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.50 (6H, m, $((\mathbf{CH_2})_3(CH_2)_2$-N); 3.51 (4H, t, *J* = 16.1, $((CH_2)_3(\mathbf{CH_2})_2$-N); 7.05-7.20 (4H, m, C_7H-C_{10}H); 7.56 (1H, s, C_5H); 8.44 (1H, s, C_2H). ^{13}C NMR spectrum, δ, ppm: 25.2 ($\mathbf{CH_2}(CH_2CH_2)_2$N); 25.7 ($CH_2(\mathbf{CH_2}CH_2)_2$N); 52.1 ($CH_2(CH_2\mathbf{CH_2})_2$N; 104.6 ($C_4$-**C**-$C_5$); 123.1 ($C_7$); 127.1 ($C_8$); 128.0 ($C_9$); 131.1 ($C_{10}$); 136.1 (S-**C**-$C_{10}$); 154.0 ($N_6$-**C**-$C_7$); 159.0 ($C_2$); 161.1 ($C_5$); 169.0 ($C_4$); 189.5 ($N_1$-**C**-$S_{10}$). Mass spectrum, *m*/*z* (*I*rel, %): 296 [M]+ (25), 28 $[CH_2CH_2]^{+\cdot}$ (100). *Anal*. Calcd. For $C_{16}H_{16}N_4S$: C, 64.84; H, 5.44; N, 18.90; S, 10.82 Found: C, 64.95; H, 5.48; N, 18.81; S, 10.35.

4-(4-Methylpiperazin-1-yl)pyrimido[4, 5- *b*][1, 5]benzothiazepine 5e

Yield 1.52 g (49%), green powder, mp 128–129°C. IR spectrum, v, cm–1: 1580 (C=N); 2960, 2900 (CH_2, CH_3). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.03 (3H, S, CH_3-N); 2.18 (4H, t, *J* = 16.1, $(\mathbf{CH_2})_2NCH_3$); 3.59 (4H, t, *J* = 16.1, $(CH_2\mathbf{CH_2})_2$N); 7.05-7.20 (4H, m, C_7H-C_{10}H); 7.56 (1H, s, C_5H); 8.44 (1H, s, C_2H). ^{13}C NMR spectrum, δ, ppm: 44.1 (N-CH_3); 46.5 ($(\mathbf{CH_2})_2NCH_3$); 56.1 ($(CH_2\mathbf{CH_2})_2$N); 104.6 (C_4-**C**-C_5); 123.0 (C_7); 127.0 (C_8); 128.1 (C_9); 131.1 (C_{10}); 136.1 (S-**C**-C_{10}); 154.0 (N_6-**C**-C_7); 159.0 (C_2); 161.1 (C_5); 169.0 (C_4); 189.5 (N_1-**C**-S_{10}). Mass spectrum, *m*/*z* (*I*rel, %): 311 [M]+ (35), 28 $[CH_2CH_2]^{+\cdot}$ (100). *Anal*. Calcd. For $C_{16}H_{17}N_5S$: C, 61.71; H, 5.50; N, 22.49; S, 10.30 Found: C, 61.57; H, 5.52; N, 22.37; S, 10.18.

4-(4-Phenylpiperazin-1-yl)pyrimido[4, 5- *b*][1, 5]benzothiazepine 5f

Yield 1.49 g (40%), green powder, mp 202–203°C. IR spectrum, v, cm–1: 1570 (C=N); 2950, 2900 (CH_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.22 (4H, t, *J* = 16.1, $(\mathbf{CH_2})_2$NPh); 3.61 (4H, t, *J* = 16.1, $(CH_2\mathbf{CH_2})_2$N); 7.02-7.53 (10H, m, Aromatic); 8.45 (1H, s, C_2H). ^{13}C NMR spectrum, δ, ppm: 46.5 ($(\mathbf{CH_2})_2NCH_3$); 56.1 ($(CH_2\mathbf{CH_2})_2$N); 104.6 (C_4-**C**-C_5); 114.1 (C_2 of Phenyl), 118.5 (C_4 of Phenyl), 123.0 (C_7); 127.0 (C_8); 128.1 (C_9); 129.3 (C_3 of Phenyl), 131.1 (C_{10}); 136.1 (S-**C**-C_{10}); 149.3 (C_1 of Phenyl), 154.0 (N_6-**C**-C_7); 159.0 (C_2); 161.1 (C_5); 169.0 (C_4); 189.5 (N_1-**C**-S_{10}). Mass spectrum, *m*/*z* (*I*rel, %): 373 [M]+ (21), 28 $[CH_2CH_2]^{+\cdot}$ (100). *Anal*. Calcd. For $C_{21}H_{19}N_5S$: C, 67.53; H, 5.13; N, 18.75; S, 8.59 Found: C, 67.69; H, 5.03; N, 18.54; S, 8.41.

***N*-Ethylpyrimido[4,5-*b*][1,5]benzothiazepin-4-amine 5g**

Yield 1.70 g (66%), green powder, mp 170–172°C. IR spectrum, v, cm^{-1}: 1570 (C=N); 2960, 2900 (CH_2, CH_3); 3350 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.02 (3H, t, *J* = 19.0, **CH_3**CH_2NH); 3.24 (2H, q, *J* = 19.0, CH_3**CH_2**NH); 7.05-7.20 (4H, m, C_7H-C_{10}H); 7.55 (1H, s, C_5H); 8.45 (1H, s, C_2H); 8.70 (1H, broad, NH). ^{13}C NMR spectrum, δ, ppm: 13.1 (**CH_3**CH_2NH); 45.2 (CH_3**CH_2**NH); 104.5 (C_4-**C**-C_5); 123.2 (C_7); 127.0 (C_8); 128.1 (C_9); 131.0 (C_{10}); 136.1 (S-**C**-C_{10}); 154.1 (N_6-**C**-C_7); 159.1 (C_2); 161.0 (C_5); 169.1 (C_4); 189.5 (N_1-**C**-S_{10}). Mass spectrum, *m*/*z* (*I*rel, %): 256 [M]+ (30), 28 [CH_2CH_2]+· (100). *Anal*. Calcd. For $C_{13}H_{12}N_4S$: C, 60.91; H, 4.72; N, 21.86; S, 12.51 Found: C, 60.73; H, 4.80; N, 21.65; S, 12.35.

N-Benzylpyrimido[4,5-*b*][1,5]benzothiazepin-4-amine 5h

Yield 2.35 g (74%), green powder, mp 185-186°C. IR spectrum, v, cm–1: 1570 (C=N); 2950, 2900 (CH_2); 3360 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.35 (2H, s, **CH_2**NHPh); 7.02-7.2 (9H, m, Aromatic); 7.55 (1H, s, C_5H); 8.45 (1H, s, C_2H); 8.70 (1H, broad, NH). ^{13}C NMR spectrum, δ, ppm: 46.2 (**CH_2**NHPh); 104.6 (C_4-**C**-C_5); 114.3 (C_2 of Phenyl), 118.7 (C_4 of Phenyl), 123.0 (C_7); 127.0 (C_8); 128.1 (C_9); 129.1 (C_3 of Phenyl), 131.1 (C_{10}); 136.1 (S-**C**-C_{10}); 149.1 (C_1 of Phenyl), 154.0 (N_6-**C**-C_7); 159.0 (C_2); 161.1 (C_5); 169.0 (C_4); 189.5 (N_1-**C**-S_{10}). Mass spectrum, *m*/*z* (*I*rel, %): 318 [M]+ (26), 28 [CH_2CH_2]+· (100). *Anal*. Calcd. For $C_{18}H_{14}N_4S$: C, 67.90; H, 4.43; N, 17.60; S, 10.07 Found: C, 67.71; H, 4.56; N, 17.34; S, 9.81.

N-Propylpyrimido[4,5-*b*][1,5]benzothiazepin-4-amine 5i

Yield 1.95 g (72%), green powder, mp 153–154°C. IR spectrum, v, cm^{-1}: 1570 (C=N); 2960, 2900 (CH_2, CH_3); 3350 (NH).

^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.00 (3H, t, *J* = 19.0, **CH_3**CH_2CH_2NH); 1.64 (2H, sextet, CH_3**CH_2**CH_2NH); 3.21 (2H, t, *J* = 19.0, CH_3CH_2**CH_2**NH); 7.05-7.20 (4H, m, C_7H-C_{10}H); 7.55 (1H, s, C_5H); 8.45 (1H, s, C_2H); 8.70 (1H, broad, NH). ^{13}C NMR spectrum, δ, ppm: 11.5 (**CH_3**CH_2CH_2NH); 23.5 (CH_3**CH_2**CH_2NH); 47.5 (CH_3CH_2**CH_2**NH); 104.6 (C_4-**C**-C_5); 123.1 (C_7); 127.0 (C_8); 128.0 (C_9); 131.0 (C_{10}); 136.1 (S-**C**-C_{10}); 154.1 (N_6-**C**-C_7); 159.1 (C_2); 161.0 (C_5); 169.1 (C_4); 189.5 (N_1-**C**-S_{10}). Mass spectrum, *m*/*z* (*I*rel, %): 284 [M]+ (22), 28 [CH_2CH_2]+· (100). *Anal*. Calcd. For $C_{15}H_{16}N_4S$: C, 63.35; H, 5.67; N, 19.70; S, 11.28 Found: C, 63.22; H, 5.61; N, 19.58; S, 11.15.

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Keywords: 4,6-Dichloropyrimidine-5-carbaldehyde, 2-aminobenzenethiol, pyrimido[4,5-*b*][1,5]benzothiazepine, cyclocondensation, fused benzothiazepines.

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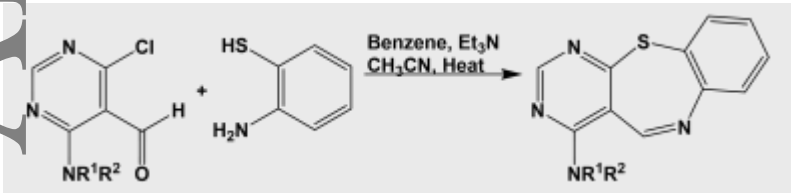

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