Synthesis of Novel Fused Pyrido Diimino Pyrimido Pyrimido derivatives Incorporating Benzothiazole Compounds

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Abstract: Novel heterocyclic compounds 13,14 di-imino pyrido[1,2-a] pyrimido [5,6-e]pyrimido[2,3-b] benzothiazole and their 1/2/3/4-substituted derivatives (5a-h) have been synthesized by condensing 3-cyano-4-imino-2-(methylthio)4H-pyrido [1,2-a] pyrimidine (3) with 2-amino 1/2/3/4 -substituted benzothiazole (4).

Keywards: N,N-dimethyl formamide, potassium carbonate, pyrido[1,2-a] pyrimidine & 2-amino benzothiazole.

Introduction :

The synthesis of pyrido[1,2-a]pyrimidine and their derivatives remains of great interest in organic chemistry, because some of them exhibit significant biological and pharmacological activities, such as antifolate activity¹, antibacterial activity², tyrosine kinase activity³, antimicrobial activity⁴, calcium channel antagonists activity⁵, anti-inflammatory and analgesic activity⁶, antileishmanial activity⁷, tuberculostatic activity⁸,anticonvulsants activity⁹, diuretic and potassium-sparing activity¹⁰, antiaggressive activity¹¹, antitumor activity¹². A number of methods have been developed for the synthesis of pyrido pyrimidine derivatives¹³-¹⁶, which usually required longer time, complex synthetic pathways, expensive catalyst and often used organic solvent. Hetero fused pyrimidines exhibit promising, anti-AIDS¹⁷ and antinoiceptive¹⁸. Thus the pursuance of more convenient and practical synthetic methods for these compounds still remains an active research area.

In our continued interest in the development of highly expedient methods for the synthesis of 13,14 diimino pyrido[1,2-a] pyrimido [5,6-e] pyrimido[2,3-b] benzothiazole and their1/2/3/4-substituted derivatives. (5) by using 3-cyano-4-imino-2-(methylthio)4H-pyrido [1, 2-a] pyrimidine (3) and 2-Amino1/2/3/4-substituted benzothiazole (4) by refluxing N,N-dimethyl formamide (DMF) and catalytic amount of anhydrous potassium carbonate with new method and improved yield.

Result and Discussion :

In the present investigation, we have developed new methodology towards the synthesis of 13,14 di-imino pyrido[1,2-a] pyrimido[5,6-e] pyrimido[2,3-b] benzothiazole and their1/2/3/4-substituted derivatives. (5) Our method gives single product with high yield. The reaction started with 2 amino pyridines (1) and bis (methylthio) methylene malonitrile (2) were refluxed in N,N-dimethyl formamide (DMF) in presence of catalytic
amount of anhydrous potassium carbonate to afford (3) Scheme-1.
The compound (3) possess replaceable active methylthio group at 2- position which is activated by the ring 1-nitrogen atom, electron withdrawing 3-cyano group. Compound (3) was reacting with 2-amino 1/2/3/4 substituted benzothiazole(4) in presence of N,N-dimethyl formamide (DMF) and catalytic amount of anhydrous potassium carbonate afforded the compound (5) subsequently, compound (3) independently heating with 2-amino benzothiazole, 2-amino 6-methyl benzothiazole,2-amino 6-methoxy benzothiazole, 2-amino 6-chlorobenzothiazole, 2-amino 6-nitro benzothiazole, 2-amino 4,6 dimethyl benzothiazole, 2-amino 7-chloro,6-floro benzothiazole, 2-amino 6,7-dimethyl benzothiazole to obtain13,14 diimino pyrido[1,2-a]pyrimido[5,6-e] pyrimido [2,3-b] benzothiazole and their1/2/3/4-substitued derivatives respectively Scheme-2.

The structure of these newly synthesized compounds were established on the basis of elemental analysis, IR, PMR and MASS Spectral data , spectral studies of all compounds shows that compounds are stable & do not exhibit any tautomerism.

\[
\begin{align*}
\text{(1)} & \quad \begin{array}{c}
\text{NH}_2 \\
\text{H}_3\text{CS} \\
\text{SCH}_3 \\
\text{NC} \\
\text{CN} \\
\end{array} \\
\text{(2)} & \quad \begin{array}{c}
\text{DMF / Anhy.} \text{K}_2\text{CO}_3 \\
\text{-CH}_3\text{SH} \\
\text{N} \\
\text{NC} \\
\text{CN} \\
\text{SCH}_3 \\
\end{array} \\
& \quad \begin{array}{c}
\text{N} \\
\text{SCH}_3 \\
\text{CN} \\
\end{array}
\end{align*}
\]

Scheme-1

<table>
<thead>
<tr>
<th>Comp. No</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
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<tbody>
<tr>
<td>5a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>5b</td>
<td>H</td>
<td>CH₃</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>5c</td>
<td>H</td>
<td>OCH₃</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>5d</td>
<td>H</td>
<td>Cl</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>5e</td>
<td>H</td>
<td>NO₂</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>5f</td>
<td>H</td>
<td>CH₃</td>
<td>H</td>
<td>CH₃</td>
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<tr>
<td>5g</td>
<td>Cl</td>
<td>F</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>5h</td>
<td>CH₃</td>
<td>CH₃</td>
<td>H</td>
<td>H</td>
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Experimental Section:
Melting point were determined by open capillary tubes and were uncorrected. All the reactions monitored by thin layer chromatography, carried out on 0.2 mm silica gel-C plates using iodine vapors for detection. Infrared spectra were recorded in Nujol or as potassium bromide pallets on infrared spectrophotometer, nuclear magnetic resonance spectra were obtained on brukner advance spectrophotometer 400 MHz mass spectra were recorded on FT-VC-7070 H Mass spectrometer using the EI technique at 70 ev. All the reaction were carried out under ambient atmosphere. Elemental analysis was performed on a Heraeus CHN-O rapid analyzer.

General procedure:
3-cyano-4-imino-2-(methylthio)4H-pyrido [1, 2-a] pyrimidine (3):
A mixture of 2-aminopyridine (2) (0.01 mol) and bis (methylthio) metylene malanonitrile (1) (0.01 mol) in 15 mL of N, N' -dimethyl formamide and anhydrous potassium carbonate (10mg) was refluxed for 5 hours. The reaction mixture was cooled to room temperature and poured into ice cold water. The separated solid product was filtered, washed with water and recrystallized from a N, N'-dimethyl formamide- ethanol mixture to give pure (3).
13,14 di-imino pyrido[1,2-alpyrimido[5,6-e]pyrimido[2,3-b]benzothiazole and their1/2/3/4- substuited derivatives (5a-h) :
A mixture of (3)(0.001mol)and independently with (4) 2-amino 6H-benzothiazole, 2-amino 6-methyl benzothiazole, 2-amino 6-methoxy benzothiazole, 2-amino 6-chloro benzothiazole, 2-amino 6-nitro benzothiazole, 2-amino 4,6 dimethyl benzothiazole, 2-amino 7,6-chloro, floro benzothiazole, 2-amino 7,6 dimethyl benzo thiazole (0.001mol) in 15 mL of N, N'- dimethyl formamide and anhydrous potassium carbonate (10mg) was refluxed for 5 hours. The reaction mixture was cooled to room temperature and poured in to ice cold water. The separated solid product was filtered, washed with water and recrystallized from a N, N'- dimethyl formamide- ethanol mixture to give pure (5a-h).

3-cyano4-imino-2-(methylthio) 4H-pyrido [1,2-alpyrimidine (3) : Orange powder, yield 60 %, mp 230 °C (dec.). IR (KBr / cm⁻¹) 3350 (=NH), 2225 (CN); 1H NMR (400 MHz,DMSO-d₆) 2.59 (s, 3H, SCH), 7.3-7.4 (d, 2H), 7.8-7.9 (m, 2H), 9.2 ( br s, 1H, =NH). EI-MS (m/z: RA %): 217 (M+I , 100%), 215 (35). 13C NMR (300 MHz, CDCl3) δ: 18.22, 40, 82, 115,120,128,130,145,149,152, 170. Anal. Calcd. For: C₁₀H₉N₄S ; C, 60.35; H, 3.55; N, 24.85. Found: C, 60.30; H, 3.50; N, 24.80.

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Table no. 2: Physical and Spectral analysis of compound (5a-h)

<table>
<thead>
<tr>
<th>Comp.no</th>
<th>M.P (°C)</th>
<th>Yield (%)</th>
<th>IR</th>
<th>MASS</th>
<th>¹H NMR</th>
</tr>
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<tbody>
<tr>
<td>5a</td>
<td>172</td>
<td>67</td>
<td>3350(=NH),3260(=NH) 2225 (CN);</td>
<td>EI-MS(m/z:RA%): 319(M+1) 291, 278,242,229,216, (100%)</td>
<td>7.0-7.6(m,8H), Ar -H 9.2-8.0(br s,2H,=NH).</td>
</tr>
<tr>
<td>5b</td>
<td>180</td>
<td>72</td>
<td>3375(=NH),3245(=NH) 2260 (CN);</td>
<td>EI-MS(m/z:RA%): 348(M)321,302,283,262,242, 229,216,199,183, 180,165(100%) 151,137,122,110, 95,78,69,45</td>
<td>7.0-7.6(m,7H), Ar –H 2.0-2.3 (m,3H), 9.2-8.1 (br s, 2H, =NH).</td>
</tr>
<tr>
<td>5c</td>
<td>165</td>
<td>80</td>
<td>3345(=NH),3220(=NH) 2225 (CN);</td>
<td>EI-MS(m/z:RA%): 348(M)302,281, 244,216(100%)192,156</td>
<td>5.2 -6.6(m,7H), Ar -H 3.0-3.7 (m,3H), 9.1-8.2 (br s, 2H, =NH).</td>
</tr>
<tr>
<td>5d</td>
<td>160</td>
<td>64</td>
<td>3370(=NH),3230(=NH) 2240 (CN);</td>
<td>EI-MS(m/z:RA%): 353(M+1)306,286, 242,216(100%)</td>
<td>---------</td>
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<tr>
<td>5e</td>
<td>Above300</td>
<td>85</td>
<td>3366(=NH),3245(=NH) 2256 (CN);</td>
<td>EI-MS(m/z:RA%): 363(M)302,274,262, 231,216(100%)</td>
<td>---------</td>
</tr>
<tr>
<td>5f</td>
<td>167</td>
<td>78</td>
<td>3335(=NH),3238(=NH) 2238 (CN);</td>
<td>EI-MS(m/z:RA%): 346(M)274,273,262, 238,216(100%)</td>
<td>5.2-7.0 (6H) Ar-H, 2.0-2.5, (6H), 9.1 (=NH), 8.0, (=NH),</td>
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<tr>
<td>5g</td>
<td>163</td>
<td>88</td>
<td>3368(=NH),3232(=NH) 2269 (CN);</td>
<td>EI-MS(m/z:RA%): 371(M+1)319, 273, 241,225,217,215, 179,169,153,(100%) 145,137,130,117</td>
<td>7.0-7.6(m,7H), Ar -H 7.8-7.9 (m,2H), 9.2-8.1 (br s, 2H, =NH).</td>
</tr>
<tr>
<td>5h</td>
<td>168</td>
<td>75</td>
<td>3353(=NH),3272(=NH) 2280 (CN);</td>
<td>---------</td>
<td>7.0-7.6(m,7H), Ar -H 7.8-7.9 (m,2H), 9.2-8.1 (br s, 2H, =NH).</td>
</tr>
</tbody>
</table>
References:

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