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

Sambhaji P. Vartale*, Nilesh K. Halikar, Nagesh D. Kalyankar, Shivraj B. Sirsat, Yogesh D Pawar &Avinash V. Pawde

P.G. Research Centre, Department of Chemistry, Yeshwant Mahavidyalaya, Nanded-431602(MS)India.

***Corres.author:** *spvartale@rediffmail.com*.

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-substuited 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 -substuited 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 activity[1], antibacterial activity[2], tyrosine kinase activity[3], antimicrobial activity[4], calcium channel antagonists activity[5], anti-inflammatory and analgesic activity[6], antileishmanial activity[7], tuber-culostatic activity[8],anticonvulsants activity[9], diuretic and potassium-sparing activity[10], antiaggressive activity[11], antitumor activity[12]. A number of methods have been developed for the synthesis of pyrido pyrimidine derivatives[13-16], which usually required longer time, complex synthetic pathways, expensive catalyst and often used organic solvent. Hetero fused pyrimidines exhibit promising, anti-AIDS [17] and antinociceptive[18].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-substuited 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.

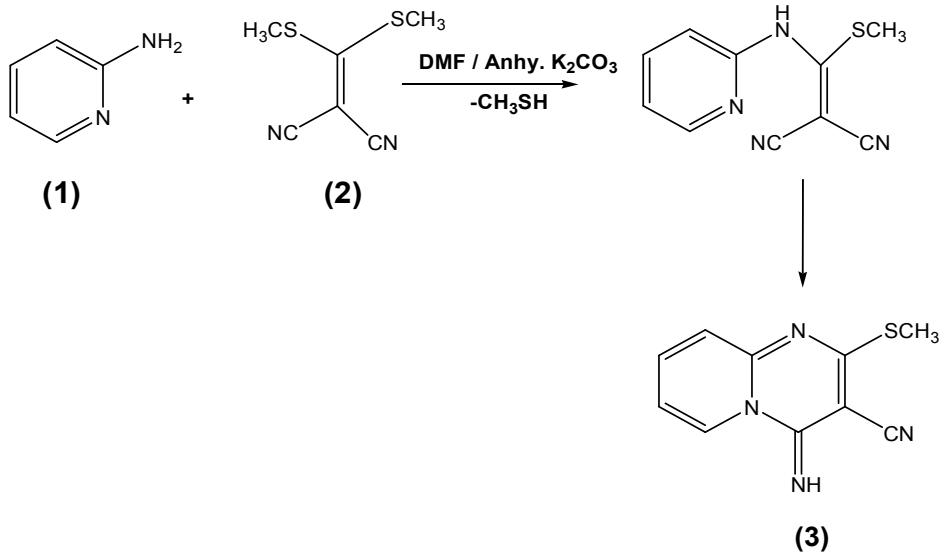
Result and Discussion :

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-substuited derivatives. **(5)** Our method gives single product with high yield. The reaction started wi th 2 amino pyridines **(1)** and bis (methylthio) methylene malanonitrile **(2)** were refluxed in N,N-dimethyl formamide (DMF) in presence of catalytic

amount of anhydrous potassium carbonate to afford **(3)** Scheme-1.

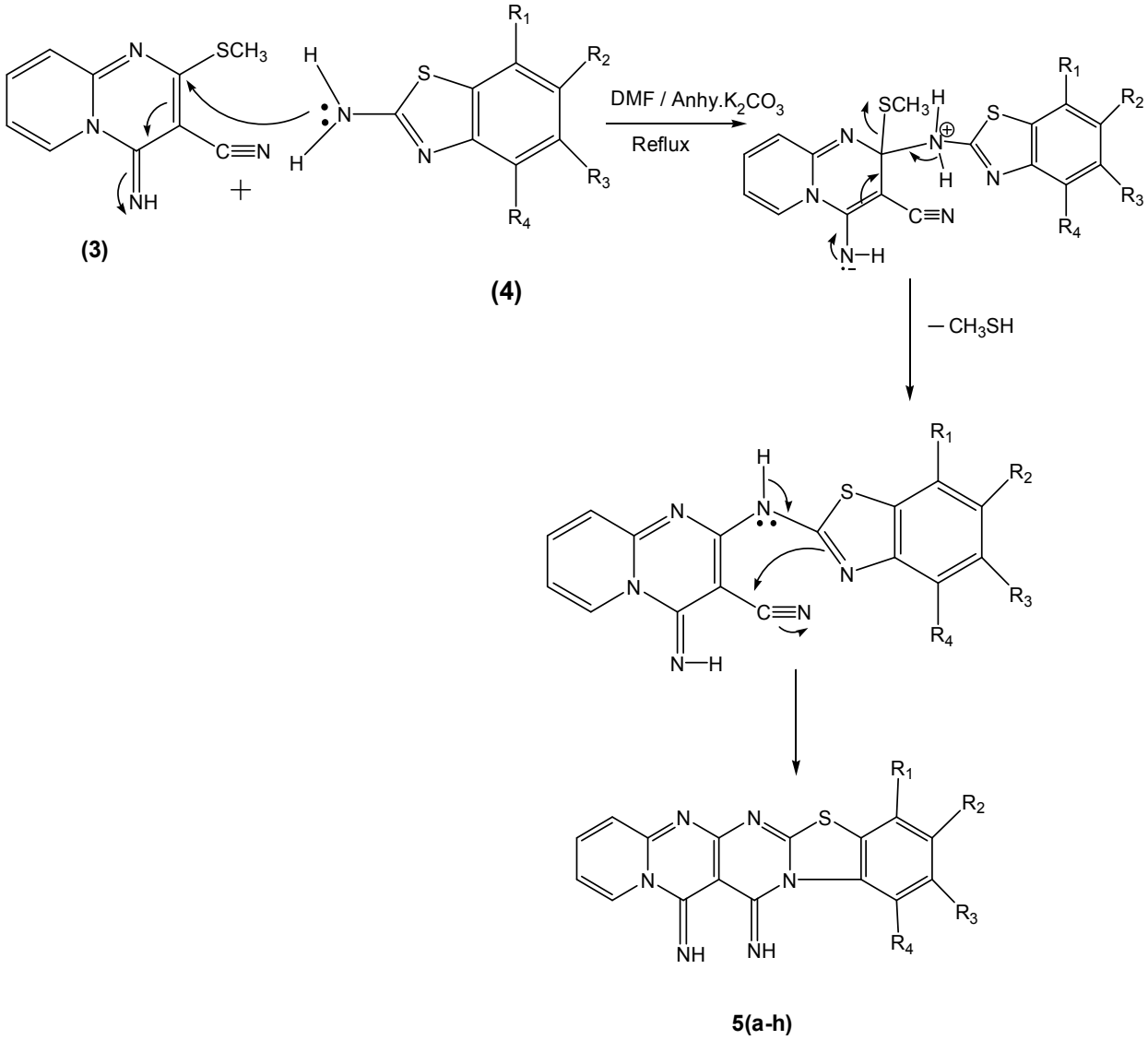
The compound **(3)** possess replaceable active methylthio group at 2- position which is activated by the ring 1-nitrogen atom, electron withdrawing 3-cyano group. Compound **(3)** was reacting with 2-amino 1/2/3/4 substituted benzothiazole**(4)** in presence of N,N-dimethyl formamide (DMF) and catalytic 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 benzoth-iazole, 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-substuited 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.



Scheme-1

Comp. No	R_1	R_2	R_3	R_4
5a	H	H	H	H
5b	H	CH_3	H	H
5c	H	OCH_3	H	H
5d	H	Cl	H	H
5e	H	NO_2	H	H
5f	H	CH_3	H	CH_3
5g	Cl	F	H	H
5h	CH_3	CH_3	H	H



Scheme-2

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 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 **(3).**

13,14 di-imino pyrido[1,2-a]pyrimido[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 benzo thiazole, 2-amino 6-methoxy benzothiazole,2-amino 6-chloro benzothiazole,2-amino 6-nitro benzothiazole, 2-amino 4,6 dimethyl benzothiazole,2-amino7,6-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-*a*]pyrimidine (3) : Orange powder, yield 60 %, mp 230 °C (dec.). IR (KBr / cm^{-1}) 3350 (=NH), 2225 (CN); 1H NMR (400 MHz,DMSO-d_6) 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: $C_{10}H_8N_4S$; 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)

Comp.no	M.P (0^0C)	Yield (%)	IR	MASS	^{1}H NMR
5a	172	67	3350(=NH),3260(=NH) 2225 (CN);	EI-MS(m/z:RA%): 319(M+1) 291, 278,242,229,216, (100%)	7.0-7.6(m,8H), Ar -H 9.2-8.0(br s,2H,=NH).
5b	180	72	3375(=NH),3245(=NH) 2260 (CN);	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	7.0-7.6(m,7H), Ar –H 2.0-2.3 (m,3H), 9.2-8.1 (br s, 2H, =NH).
5c	165	80	3345(=NH),3220(=NH) 2225 (CN);	EI-MS(m/z:RA%): 348(M)302,281, 244,216(100%)192, 156	5.2 -6.6(m,7H), Ar -H 3.0-3.7 (m,3H), 9.1-8.2 (br s, 2H, =NH).
5d	160	64	3370(=NH),3230(=NH) 2240 (CN);	EI-MS(m/z:RA%): 353(M+1)306,286, 242,216(100%)	----------
5e	Above300	85	3366(=NH),3245(=NH) 2256 (CN);	EI-MS(m/z:RA%): 363(M)302,274,262, 231,216(100%)	
5f	167	78	3335(=NH),3238(=NH) 2238 (CN);	EI-MS(m/z:RA%): 346(M)274,273,262, 238,216(100%)	5.2-7.0 (6H) Ar-H, 2.0-2.5,(6H), 9.1 (=NH) , 8.0,(=NH),
5g	163	88	3368(=NH),3232(=NH) 2269 (CN);	EI-MS(m/z:RA%): 371(M+1)319, 273, 241,225,217,215, 179,169,153,(100%) 145,137,130,117	7.0-7.6(m,7H), Ar -H 7.8-7.9 (m,2H), 9.2-8.1 (br s, 2H, =NH).
5h	168	75	3353(=NH),3272(=NH) 2280 (CN);	----------	7.0-7.6(m,7H), Ar -H 7.8-7.9 (m,2H), 9.2-8.1 (br s, 2H, =NH).

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