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RESEARCH ARTICLE

Synthesis and Characterization of Fused Pyrimido-pyrimidine Dicarbonitriles and their Antibacterial Activity

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Abstract: Novel heterocyclic compounds containing pyrimido-pyrimidine moiety have been synthesized by the reaction of 2,4-diamino-6-(4'-substituted phenyl)pyrimidine-5-carbonitrile with bis-(-methylthio)methylene malanonitrile in presence of anhydrous K_2CO_3 to yield 6-amino-4-imino-8-(-4'-substituted phenyl)-2-(methylthio) 4(H) pyrimido[1,2-b]pyrimidine-3,7-dicarbonitrle. The structure of pyrimido-pyrimidine dicarbonitriles have been characterized by using IR and ^{1}H NMR spectroscopy. These compounds were screened for their antibacterial activity.

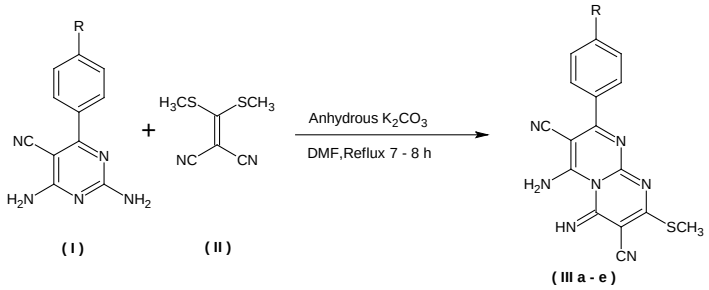
Keywords: 2,4-Diamino-6-(4'-substituted phenyl)pyrimidine-5-carbonitrile, Bis-(methylthio)-methylene malanonitrile, Anhydrous K_2CO_3, Antibacterial activity, Penicillin

Introduction

In the last few years researchers have been highly interested in the chemistry of heterocyclic derivatives with their expected biological activity[1-3]. Earlier of this fused pyrimido benzothiazole possessing three to four rings[4-6] have been reported, which exhibit the activities like Anti-inflammatory[7], antiallergic[8], antitumer[9] and antiparakinsonism[10] some pyrimidine derivatives showed antihypertensive, antipyretics, analgesics[11] activity.

Few pyrimidine derivatives are pesticides[12], herbicides and plant growth regulators[13]. Synthetic methodologies for the synthesis of novel fused pyrimido-pyrimidine nuclous have better interest in pharmaceutical and biological activity, particularly in cancer research.

In this route, we report the novel heterocyclic system possessing fused two rings. 6-Amino-4-imino-8-(4'substituted phenyl)-2-(methylthio)-4(H) pyrimido[1,2-b]pyrimidine-3,7-dicarbonitrile (III) was synthesized from 2,4 diamino-6-(-4'-substituted phenyl) pyrimidine-5-carbonitrile (I)[14] with bis-(methyl thio)methylene malanonitrile (**II**) in DMF solvent in presence of anhydrous K_2CO_3.



Scheme 1

Experimental

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected (Table 1). All products were monitored by TLC using Merck silica gel for TLC. IR spectra were measured on SHIMADZU FTIR spectrometer. ^{1}H NMR spectra were recorded on a BRUKER DRX 300 A.V. ANCE spectrometer at 300 MHz. Mass spectra was recorded on a SHIMADZU QP1100EX mass spectrometer.

*Preparation of 6-amino-4-imino-8-(4'-substituted phenyl)-2-(methylthio)-4-(H) pyrimido[1,2-b]pyrimidine-3,7 dicarbonitrile (**III**$_{a-e}$)*

Mixtures of compound (**I**) (2.4 g 1 eq) and reagent compound (**II**) (1.4 g 1 eq) in 25 mL DMF was refluxed for 6-8 h in presence of anhydrous K_2CO_3. The progress of the reaction was monitored by TLC using benzene:ethyl acetate. The reaction mixture was transferred into ice cold water, solid gets separated out and recrystallized from ethanol (Scheme 1). The yield is shown in Table 2.

Table 1. Physical data and elemental analysis

R	Compd.	Mol. formula	Mol. Wt	M.P. ^oC	Yield %	Elemental analysis %	
						Calculated	Found
H	**III$_a$**	$C_{16}H_{11}N_7S$	333	260	60	C=57.65, H=3.30 N=29.42, S=9.60	C=57.70, H=3.31 N=29.40, S=9.61
OMe	**III$_b$**	$C_{17}H_{13}N_7SO$	363	240	85	C=56.19, S=8.81 N=26.99, H=3.58, O=4.40	C=56.20, S=8.85 N=26.99,H=3.59, O=4.40
CH_3	**III$_c$**	$C_{17}H_{13}NS$	347	210	72	C=58.78,N=28.24, H=3.74, S=9.22	C=58.78,N=28.24, H=3.75, S=9.25
Cl	**III$_d$**	$C_{16}H_{10}N_7SCl$	367	250	50	C=52.31,N=26.70, H=2.72, S=8.71, Cl=9.67	C=52.30,N=26.71, H=2.73, S=8.72, Cl=9.68
NO_2	**III$_e$**	$C_{16}H_{10}N_7SO_2$	364	260	62	C=52.74,N=26.92, O=8.79, S=8.79, H=2.74	C=52.75,N=26.92, O=8.80, S=8.80, H=2.74

Table 2. Reaction time and yield

Compounds	R	Reflux Time, h	Yield, %
III$_a$	H	7	60
III$_b$	Ome	6	85
III$_c$	CH_3	6-7	72
III$_d$	Cl	8	50
III$_e$	NO_2	8	62

Spectral analysis

*6-Amino-4-imino-8-phyenyl-2-(methylthio)-4(H)pyrimido[1,2-b]pyrimidine3-7, dicarbonitrile (**III$_a$**)*

Red brown crystals; mp= 260 ^oC, IR: υ_{max} (KBr) 3380, 3329 (NH_2), 2210 (CN), 1680 (C=N), 2980,2850 ($-CH_3$) 1620, 1580,1540 (Ar) cm^{-1}; ^1H NMR: (300 MHz, DMSO-d6) δ 2.5 s (3H), 4.2 s (NH_2), 6.8-7.5 m (Ar-H). MS, *m/z*, 330 (M-2, NH_2) & (M-1,NH).

*6-Amino-4-imino-8-(4'-methoxy phenyl)-2-(methylthio)-4(H) pyrimido[1,2-b]-pyrimidine 3-7, dicarbonitrile (**III$_b$**)*

Red brown colour; mp= 240 ^oC, IR: υ_{max} (KBr) 3401,3350 (NH_2), 2202 (-CN),1630 (C=N), 2995,2890 ($-CH_3$) 1590, 1550,1420 (Ar-H)cm^{-1}; ^1H NMR: δ 2.19 s (3H), 3.63 s (3H), 4.5 s (NH_2), 6.5-7.9 m (Ar-H). MS, *m/z*, 330 (*m*-OCH_3 & M-NH_2).

*6-Amino-4-imino-8-(4'-methyl phenyl)-2-(methylthio)-4(H) pyrimido[1,2-b]pyrimidine 3,7, dicarbonitrile (**III$_c$**)*

Mp= 210 ^oC, IR: υ_{max} (KBr) 3412, 3380 ($-NH_2$), 2950, 2890 (CH_3), 2215 (CN), 1625 (C=N), 1620,1580,1400 (Ar-H); ^1H NMR: δ 2.25 s (3H), 2.95 s (3H), 4.31 s (NH_2), 6.8-7.9 m (Ar-H).

*6-Amino-4-imino-8-(4'-chlorophenyl)-2-(methylthio)-4(H) pyrimido[1,2-b]pyrimidine 3,7, dicarbonitrile (**III$_d$**)*

Mp=250 ^oC, IR: υ_{max} (KBr) 3401, 3350 ($-NH_2$), 2960,2850 (CH_3), 2220 (CN), 1630 (C=N), 1615,1590,1510 (Ar-H); ^1H NMR: δ 2.30 s (3H), 4.1 s (NH_2), 6.5-7.6 m (Ar-H).

*6-Amino-4-imino-8-(4'-Nitrophenyl) 2-(methylthio) 4(H) pyrimido[1,2-b]pyrimidine 3,7, dicusbonitrile (**III$_e$**)*

Yellow crystal, mp=260 ^oC, IR: υ_{max} (KBr) 3409,3380 ($-NH_2$), 2981,2850 ($-CH_3$), 2210 (CN), 1640 (C=N), 1625,1595,1520 (Ar-H),1518,1420 ($-NO_2$) ^1H NMR: δ 2.10 s (3H), 4.5 (NH_2), 6.6-7.8 m (Ar-H).

Results and Discussion

Reaction of bis(methylthio)methylene malanonitrile (**II**) (1 eq.) with 2.4 diamino-6-(4'-substituted phenyl)pyrimidine-5-carbonitrile (**I**) (1.eq) in presence of anhydrous K_2CO_3 and DMF as solvent was carried out under reflux for 7-8 hours to yield compound **III$_{a-e}$**.

The compound (**I**) having 2,4-diamino functional group but amino group at 2nd position become free from steric hindrance, under maintained condition and equivalent ratio monocyclisation occurs to form compound **III$_{a-e}$**. After spectral studies monocyclised compounds were found and the yield of compounds is shown in the Table 2.

Antibacterial activity

The synthesized compounds were screened for their antibacterial activity against gram positive species *S.aureus* and *B.substilis* and gram-negative species *E.coli* and *S.typhi* by paper disc diffusion method[15]. All the synthesized compounds were dissolved in dimethyl formamide (DMF). The synthesized compounds showed zone of inhibition from 8-14 mm in diameter, whereas standard streptomycin exhibit zone of inhibition is 16 and 20 mm in diameter against *S. aureus* and *B.substilis* and penicillin exhibited zone of inhibition is 13 &

16 mm in diameter against *E.coli* and *S.typhi* respectively. Among all synthesized compounds $\mathbf{III_{a-e}}$, compound $\mathbf{III_d}$ (12,10,12,13) and compound $\mathbf{III_b}$ (09,11,11,14) showed higher zone of inhibition against *S.aureus*, *B.substilis*, *E.coli* and *S.typhi* respectively (Table 3). Our conclusion about present work showed that presence of halogen (Cl) and methoxy (OCH_3) group at 4'-position increases the antibacterial activity.

Table 3. Antibacterial activity of compounds ($\mathbf{III_{a-e}}$)

Compd.	Zone of inhibitation in dimeter in mm at 25 µg/disc			
	S.aureus	*B.substilis*	*E.coli*	*S.typhi*
$\mathbf{III_a}$	09	10	08	09
$\mathbf{III_b}$	09	11	11	14
$\mathbf{III_c}$	08	10	09	12
$\mathbf{III_d}$	12	10	12	13
$\mathbf{III_e}$	11	09	08	10
Streptomycin	16	20	-	-
Penicillin	--	-	13	16

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