

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-dicarbonitrile. The structure of pyrimido-pyrimidine dicarbonitriles have been characterized by using IR and 1H NMR spectroscopy. These compounds were screened for their antibacterial activity.

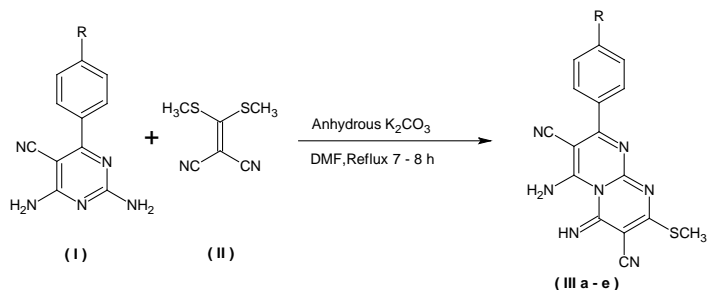
Keywords: 2,4-Diamino-6-(4'-substituted phenyl)pyrimidine-5-carbonitrile, Bis-(methylthio)-methylene malanonitrile, Anhydrous K_2CO_3 , Antibacterial activity, Penicillin

Introduction

In the last few years researchers have been highly interested in the chemistry of heterocyclic derivatives with their expected biological activity¹⁻³. Earlier of this fused pyrimido benzothiazole possessing three to four rings⁴⁻⁶ have been reported, which exhibit the activities like Anti-inflammatory⁷, antiallergic⁸, antitumor⁹ and antiparkinsonism¹⁰ some pyrimidine derivatives showed antihypertensive, antipyretics, analgesics¹¹ activity.

Few pyrimidine derivatives are pesticides¹², herbicides and plant growth regulators¹³. Synthetic methodologies for the synthesis of novel fused pyrimido-pyrimidine nucleus 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. ¹H NMR spectra were recorded on a BRUKER DRX 300 A.V. ANCE spectrometer at 300 MHz. Mass spectra were 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 K₂CO₃. 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. °C	Yield %	Elemental analysis %	
						Calculated	Found
H	III _a	C ₁₆ H ₁₁ N ₇ S	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 ₇ SO	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 ₇ SCl	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 ₇ SO 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-phenyl-2-(methylthio)-4(H)pyrimido[1,2-b]pyrimidine-3,7-dicarbonitrile (III_a)

Red brown crystals; mp= 260 °C, IR: ν_{\max} (KBr) 3380, 3329 (NH₂), 2210 (CN), 1680 (C=N), 2980,2850 (-CH₃) 1620, 1580,1540 (Ar) cm⁻¹; ¹H NMR: (300 MHz, DMSO-d₆) δ 2.5 s (3H), 4.2 s (NH₂), 6.8-7.5 m (Ar-H). MS, *m/z*, 330 (M-2, NH₂) & (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 °C, IR: ν_{\max} (KBr) 3401,3350 (NH₂), 2202 (-CN),1630 (C=N), 2995,2890 (-CH₃) 1590, 1550,1420 (Ar-H)cm⁻¹; ¹H NMR: δ 2.19 s (3H), 3.63 s (3H), 4.5 s (NH₂), 6.5-7.9 m (Ar-H). MS, *m/z*, 330 (m-OCH₃ & M-NH₂).

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

Mp= 210 °C, IR: ν_{\max} (KBr) 3412, 3380 (-NH₂), 2950, 2890 (CH₃), 2215 (CN), 1625 (C=N), 1620,1580,1400 (Ar-H); ¹H NMR: δ 2.25 s (3H), 2.95 s (3H), 4.31 s (NH₂), 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 °C, IR: ν_{\max} (KBr) 3401, 3350 (-NH₂), 2960,2850 (CH₃), 2220 (CN), 1630 (C=N), 1615,1590,1510 (Ar-H); ¹H NMR: δ 2.30 s (3H), 4.1 s (NH₂), 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, dicarbonitrile (III_e)

Yellow crystal, mp=260 °C, IR: ν_{\max} (KBr) 3409,3380 (-NH₂), 2981,2850 (-CH₃), 2210 (CN), 1640 (C=N), 1625,1595,1520 (Ar-H),1518,1420 (-NO₂) ¹H NMR: δ 2.10 s (3H), 4.5 (NH₂), 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 K₂CO₃ 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 method¹⁵. 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 **III_{a-e}**, compound **III_d** (12,10,12,13) and compound **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 (OCH₃) group at 4'-position increases the antibacterial activity.

Table 3. Antibacterial activity of compounds (**III_{a-e}**)

Compd.	Zone of inhibition in diameter in mm at 25 µg/disc			
	<i>S.aureus</i>	<i>B.substilis</i>	<i>E.coli</i>	<i>S.typhi</i>
III_a	09	10	08	09
III_b	09	11	11	14
III_c	08	10	09	12
III_d	12	10	12	13
III_e	11	09	08	10
Streptomycin	16	20	-	-
Penicillin	--	-	13	16

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