INTERNATIONAL JOURNAL OF CURRENT RESEARCH IN CHEMISTRY AND PHARMACEUTICAL SCIENCES
(p-ISSN: 2348-5213: e-ISSN: 2348-5221)
www.ijcrcps.com
Coden:IJCROO(USA) Volume 3, Issue 3 - 2016

Research Article

2348-5221

SOI: http://s-o-i.org/1.15/ijcrcps-2016-3-3-3

A NEW EFFICIENT SYNTHESIS OF TETRA SUBSTITUTED PYRIMIDINES AND THEIR ANTIMICROBIAL ACTIVITY

S.P. VARTALE*, B.D. KALYANKAR AND D.S. KAWALE

PG Research Center,
Department of Chemistry,
Yeshwant Mahavidyalaya Nanded-431602 (MS) India
*Corresponding Author: spvartale@gmail.com

Abstract

Synthesis of novel heterocyclic 4-amino-2-methyl-6-(methylthio)pyrimidine-5-carbonitrile (3) was prepared by condensing acetamidine hydrochloride (1) with bis(methylthio)methylene malononitrile (2) in DMF and potassium carbonate as catalyst. Compound (3) has methylthio group at sixth position, which is replaced by different nucleophiles such as substituted anilines, phenols, hetryl amines and compounds containing active methylene group to afford 6-substituted derivatives of compound (3). The newly synthesized compounds were characterized by IR, ^{1}H-NMR, Mass spectral analysis. Antimicrobial study of series of these compounds was implemented with respect to Gram positive and Gram negative micro-organisms. The result of antimicrobial activity reveals that most of the newly synthesized pyrimidine derivatives exhibit promising antimicrobial activity.

Keywords: Acetamidine hydrochloride, Bis(methylthio)methylene malononitrile, DMF, Potassium carbonate and pyrimidines.

Introduction

Pyrimidines are interesting class of nitrogen containing compound which are basically found in bio-organic and medicinal chemistry. The pyrimidine heterocyclic core is an important subunit because of its widespread abundance in the basic structure of numerous natural products[1]. The presence of pyrimidine base in thymine, cytosine and uracil which are important building blocks of nucleic acid is one possible reason for their widespread therapeutic application. It is also found in many synthetic compounds such as barbiturates and HIV drugs zidovudine. In addition to this various analogues of pyrimdines have been found to posses antibacterial[2], antifungal[3], antidiabetic[4], anti-inflammatory[5], antiallergic[6], analgesic[7], anticonvulsant[8], antipyretic[9], antiviral[10], CNS-depressant[11], herbicidal[12] and anticancer activities[13].

By survey of literature it is found that number of synthetic methods are available for the preparation of pyrimidines[14-21]. One of the best method is reaction of acetamidine hydrochloride with system containing -C=O, -C=C, -C=N, groups it gives pyrimidine, imidazolezole etc. Acetamidine hydrochloride is a di-nucleophilic in nature and efficient precursor which have been extensively utilised in heterocyclic synthesis. Ram Vishnu and co-workers reported the synthesis of 4-amino-2-methyl-6- (methylthio) pyrimidine-5-carbonitrile from acetamidine hydrochloride and bis (methylthio)methylene malononitrile[22]. Recently we reported synthesis of pyrido pyrimidines by using K_2CO_3 and DMF[23].

Keeping in view of divers antimicrobial activities of pyrimidines, it was thought to construct a novel system which may combine with bioactive rings together in same framework by different methodology. Hence as a part of our ongoing program to develop efficient and robust method for the preparation of biologically relevant

relevant substituted pyrimidines and its different derivatives. Pyrimidine was synthesized by condensation of acetamidine hydrochloride and bis(methylthio)methylene malononitrile. Further the compound was treated with different substituted nucleophiles such as aryl amines, phenols, heteryl amines and active methylene compounds to obtain 6-substituted derivatives of pyrimidines.

Material and Methods

Electrothermal IA 9000 SERIES digital melting point apparatus was used to determine the melting points of synthesized compounds and were uncorrected. Homogeneity of all the compounds were routinely checked on 0.2 mm silica gel-C plates using ethyl acetate:hexane (3:7) as irrigant. 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 in DMSO-d6 using tetramethylsilane (TMS) as internal reference, Mass spectra were recorded on FT-VC-7070 H Mass spectrometer using the EI technique.

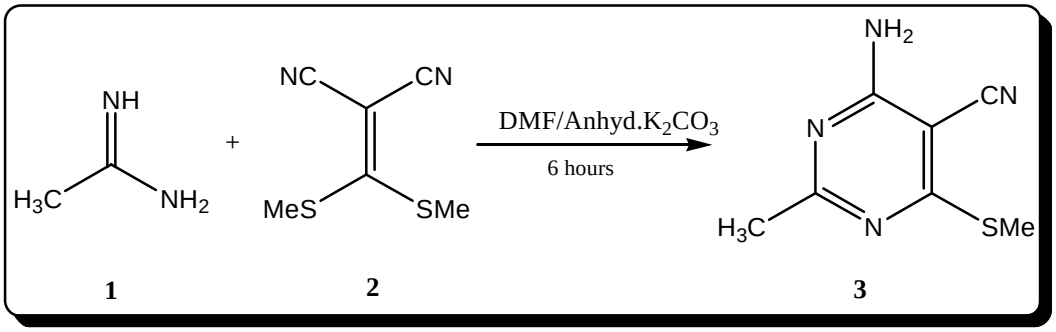
General procedure:

Synthesis of 4-amino-2-methyl-6-(methylthio) pyrimidine-5-carbonitrile (3)

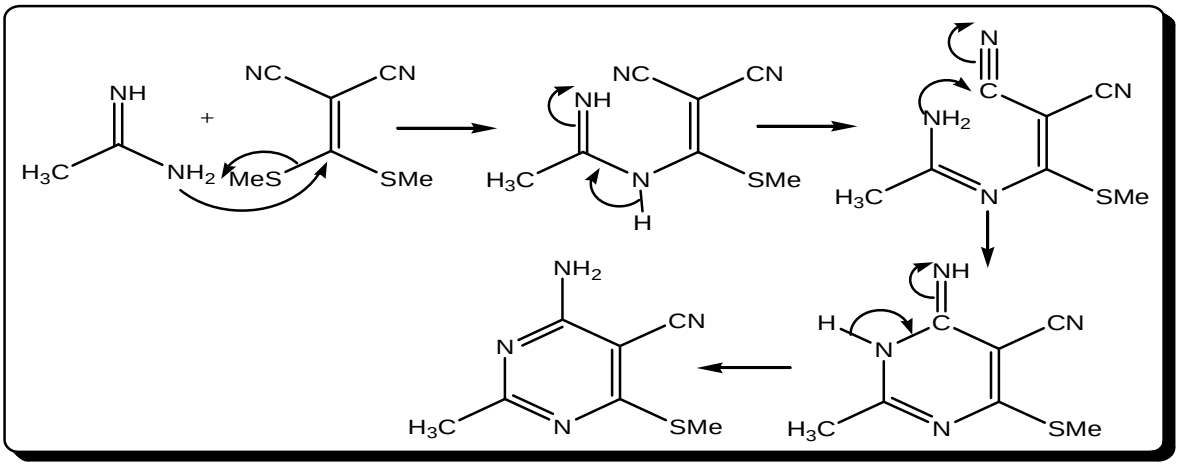
A mixture acetamidine hydrochloride (1) (0.01mol) and bis(methylthio)methylene malononitrile (2) (0.01mol) in 10 ml of DMF and anhydrous potassium carbonate (10mg) was refluxed for 6 hours. The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of reaction, the reaction mixture was cooled to room temperature and poured in to ice cold water. The separated solid product was filtered, washed with water and recrystalized from DMF-ethanol mixture to give pure compound (3).

Synthesis of 6-substituted derivative of 4-amino-2-methylpyrimidine-5-carbonitrile (4a-7d)

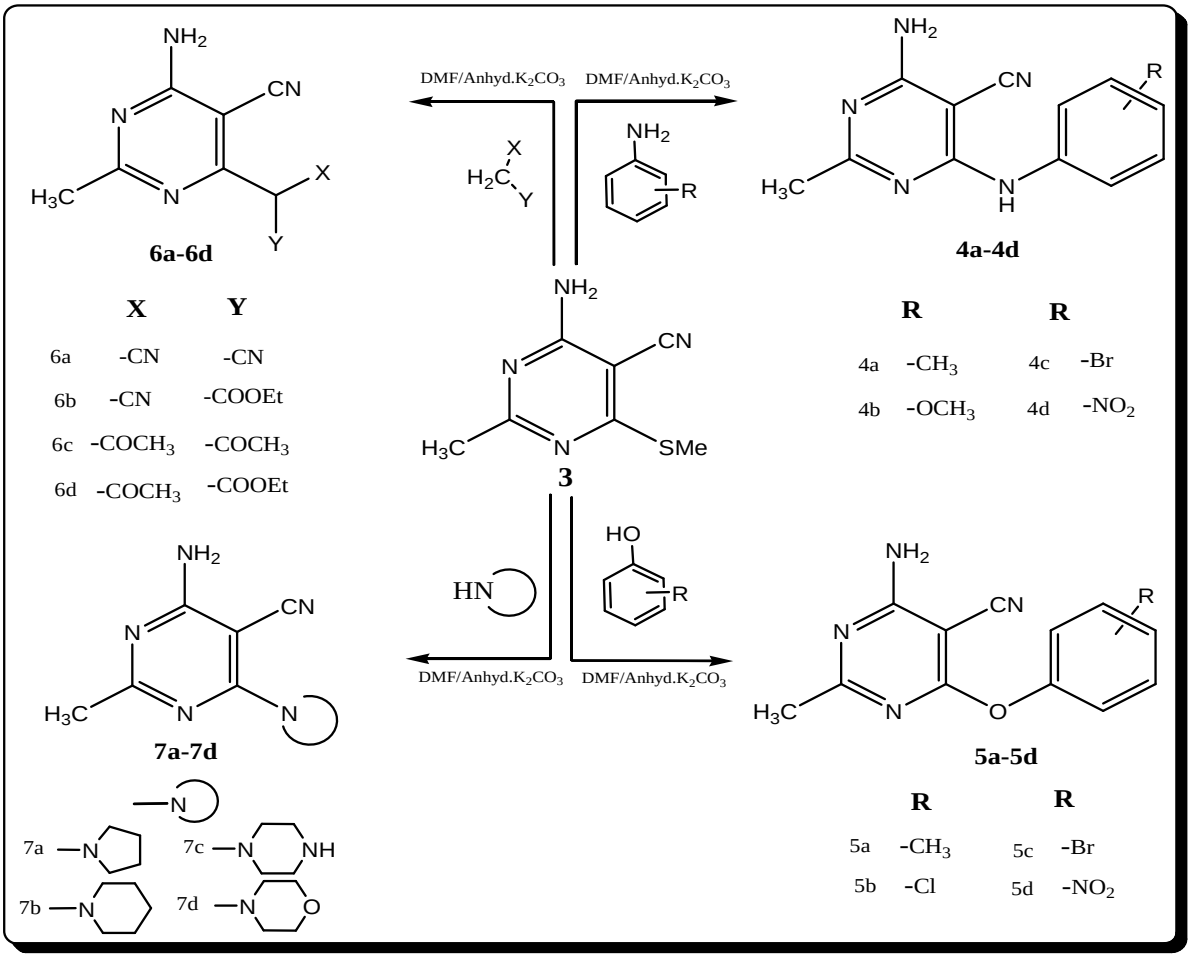
A mixture of compound (3) (0.001mol) refluxed independently with substituted anilines/ phenols/ hetryl amines/ compound containing active methylene groups (0.001mol) in 10 ml of DMF and anhydrous potassium carbonate(10mg) for 5 hours. The reaction progress was checked by TLC. The reaction mixture was cooled to room temperature and poured in to ice cold water. The separated solid product was filtered, washed with water and recrystalized from DMF-ethanol (2:8) mixture to give pure compounds (4a-4d, 5a-5d,6a-6d,7a-7d).



Scheme-1. Formation of 4-amino-2-methyl-6-(methylthio)pyrimidine-5-carbonitrile.



Scheme-1. Plausible mechanism of formation for compound (3).



Scheme-2. Formation of 6-substituted derivatives 4-amino-2-methylpyrimidine-5-carbonitrile.

Result and Discussion

In present communication we wish to report new, simple and chief method for synthesis of 4-amino-2-methyl-6-(methylthio)pyrimidine-5-carbonitrile and its 6-substituted derivatives. In our first scheme we condensed acetamidine hydrochloride (1) and bis(methylthio)methylene malononitrile (2) in DMF and catalytic amount of anhydrous K_2CO_3 to afford (3) **Scheme-1**.

The compound (3) posseses replaceable active methyl thio group which is activated by nitrogen atom, electron withdrawing cyano group. When compound (3) (1mole) was condensed independently with substituted anilines/ phenols/ hetryl amines/ compound containing active methylene groups in DMF and catalytic amount of anhydrous K_2CO_3 to afford 6-substituted derivatives of 4-amino-2-methylpyrimidine-5-carbonitrile (4a-4d,5a-5d,6a-6d,7a-7d) **Scheme-2.**

The structure of newly synthesized compounds were assigned on the basis of elemental analysis, IR,^{1}HNMR, Mass spectral data. The elemental analysis values are in good agreement with theoretical data.

Spectral Analysis:

4-amino-2-methyl-6-(methylthio)pyrimidine-5-carbonitrile (3)

IR (KBr/cm^{-1}) 2235 (CN), 3359 (NH_2): ^{1}HNMR (400 MHz,DMSO-d_6): δ = 2.38 (s, 3H, CH_3), 2.53 (s, 3H, SCH_3), 7.5 (s, 2H, NH_2): ^{13}C NMR (DMSO-d_6): δ = 11.84 (SCH_3), 25.98 (CH_3), 81.79 (C-CN), 114.54 (CN), 162.59 (C=N), 168.04 (C=N), 172.10 (C-SCH_3) EI-MS(m/z: RA%): 180 (M^+).

4-amino-2-methyl-6-(p-tolylamino)pyrimidine-5-carbonitrile (4a)

IR (KBr/cm^{-1}) 2219 (CN), 3260 (NH_2): ^{1}HNMR (400 MHz,DMSO-d_6): δ = 2.19 (s, 3H, Ar-CH_3), 2.28 (s, 3H, CH_3), 5.9-6.8(m, 4H, Ar-H), 7.20 (s, 2H, NH_2), 7.4 (s, 1H, NH): EI-MS(m/z: RA%): 239 (M^+).

4-amino-2-methyl-6-(p-tolyloxy)pyrimidine-5-carbonitrile (5a)

IR (KBr/cm^{-1}) 2245 (CN), 3273 (NH_2): ^{1}HNMR (400 MHz,DMSO-d_6): δ = 2.2 (s, 3H, Ar-CH_3), 2.31 (s, 3H, CH_3), 6.1-7.0 (m, 4H, Ar-H), 7.1 (s, 2H, NH_2): EI-MS (m/z: RA%): 240 (M^+).

4-amino-2-methyl-6-(dicyanomethyl)pyrimidine-5-carbonitrile (6a)

IR (KBr/cm^{-1}) 2218 (CN), 3370 (NH_2): ^{1}HNMR (400 MHz,DMSO-d_6): δ = 2.31 (s, 3H, CH_3), 3.24 (s, 1H, CH), 7.42 (s, 2H, NH_2): EI-MS (m/z: RA%): 198 (M^+).

4-amino-2-methyl-6-(pyrrolidine-1-yl)pyrimidine-5-carbonitrile (7a)

IR (KBr/cm^{-1}) 2254 (CN), 3342 (NH_2): ^{1}HNMR (400 MHz,DMSO-d_6): δ = 1.3 (t, 4H, CH_2), 2.8 (t, 4H, CH_2), 2.29 (s, 3H, CH_3), 7.30 (s, 2H, NH_2): EI-MS (m/z: RA%): 203 (M^+).

Spectral studies of all compounds shows that compounds were stable and do not exhibit any tautomerism. All the compounds were screened for their antibacterial activities. Investigation of antimicrobial activity it was found that 4-amino-2-methylpyrimidine-5-carbonitrile derivatives (4b), (5d) and (6c) showed higher activity against all the micro-organisms employed for antimicrobial screening.

In summary, most of our synthesized compounds showed high and moderate activity against *Bacillus subtilis, Staphylococcus aureus,* and *Salmonella typhi.*

Table 1. Physicochemical data.

Com. No.	Molecular Formula	Mol. Wt.	Colour	Yield %	M.P °C
3	$C_7H_8N_4S$	180	Gray	72.17	135-36
4a	$C_{13}H_{13}N_5$	239	Brown	65.08	207-09
4b	$C_{13}H_{13}N_5O$	255	Yellow	71.02	155-57
4c	$C_{12}H_{10}N_5Br$	303	Brown	68.94	182-84
4d	$C_{12}H_{10}N_6O_2$	270	Yellow	52.11	210-12
5a	$C_{13}H_{12}N_4O$	240	Yellow	78.53	195-96
5b	$C_{12}H_9N_4OCl$	260	Yellow	70.38	175-77
5c	$C_{12}H_9N_4OBr$	304	Brown	55.64	180-82
5d	$C_{12}H_9N_5O_3$	271	Yellow	65.41	197-98
6a	$C_9H_6N_6$	198	Brown	69.00	164-65
6b	$C_{11}H_{11}N_5O_2$	245	Brown	76.88	148-49
6c	$C_{11}H_{12}N_4O_2$	232	Brown	58.46	168-70
6d	$C_{12}H_{14}N_4O_3$	262	Brown	72.98	191-93
7a	$C_{10}H_{13}N_5$	203	Yellow	54.66	204-06
7b	$C_{11}H_{15}N_5$	217	Brown	64.08	188-89
7c	$C_{10}H_{14}N_6$	218	Brown	76.42	154-55
7d	$C_{10}H_{13}N_5O$	219	Brown	62.18	216-18

Table 2.Antimicrobial activity of compound (4a-7d)

Compounds	Gram positive		Gram negative	
	B. subtilis	***S. aureus***	***S. typhi***	***E. coli***
4a	++	++	++	-
4b	**+++**	**++++**	**++++**	**+++**
4c	++	+++	++	++
4d	+	++	++	+++
5a	+++	+++	++	++
5b	++	++	+++	++
5c	-	++	++	-
5d	**++++**	**++++**	**++++**	**+++**
6a	++	+++	++	++
6b	+++	++	++	++
6c	**++++**	**+++**	**++++**	**++++**
6d	+++	++	++	-
7a	-	++	++	+
7b	++	+++	+++	++
7c	+	++	++	++
7d	++	+++	+++	++
Streptomycin	**++++**	**-**	**-**	**++++**
Penicillin		**++++**	**++++**	

Note: (-) indicate no antimicrobial activity, (+) weak activity with inhibition 01-06 mm, (++) slight activity with inhibition 07-12 mm, (+++) moderate activity with inhibition 13-18 mm and (++++) high activity with inhibition 19-24 mm.

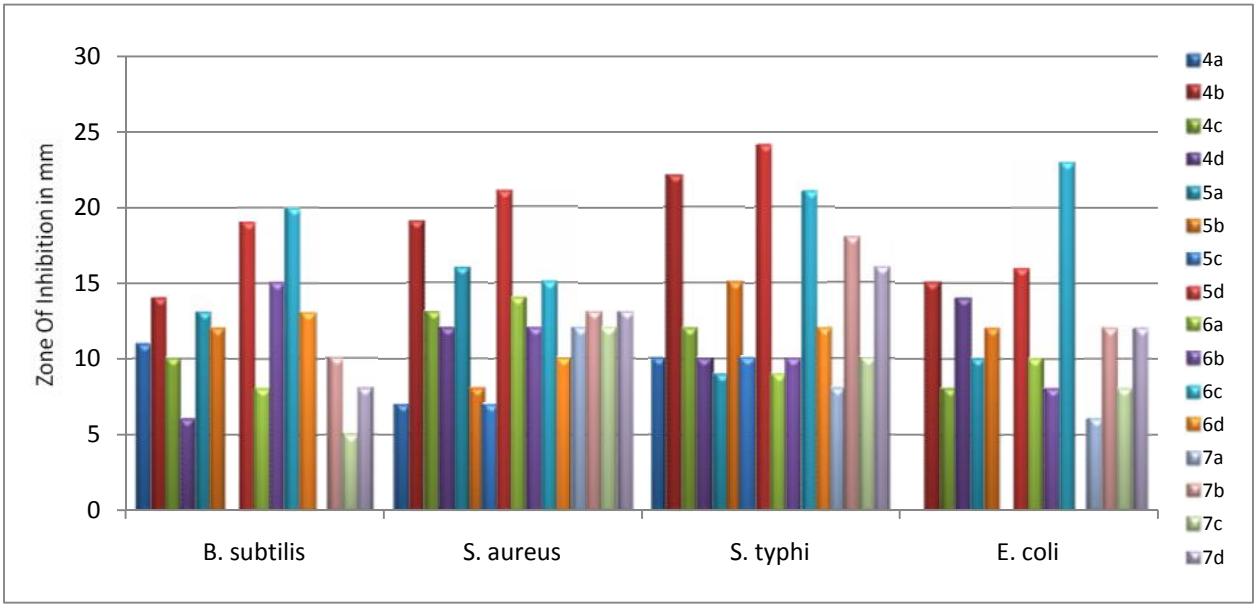


Fig.1: Comparative Antimicrobial activity of compounds 4a-7d.

Antimicrobial Activity

All synthesized compounds were evaluated for their antimicrobial screening against different pathogenic micro-organisms (gram +ve and gram -ve) such as *Bacillus subtilis, Staphylococcus aureus, Salmonella typhi, Escherichia coli.* The technique used in this experiment was paper disk diffusion method. To studying the activities of these compounds streptomycin and penicillin were used as standard drugs. All the compounds were dissolved in dimethyl sulphoxide (100µg/ml in DMSO). For bacterial growth incubation period was 24 hours at temperature 37°c. Activity of compounds was determined by measuring the diameter of zone of inhibition, values obtained was compared with the values produced from standard drugs like streptomycin and penicillin. From all synthesized compounds (4b), (5d) and (6c) shows comparative activity with standard drugs (streptomycin and penicillin). The newly synthesized compounds show zone of inhibition 5-24 mm in diameter where as standard streptomycin exhibit zone of inhibition 19-24 mm in diameter.

Conclusion

This work describe proficient and absulute method for the synthesis of novel heterocyclic compounds such as 4-amino-2-methyl-6-(methylthio)pyrimidine-5-carbonitrile and its 6-substituted derivatives of by simple and efficient route with good product yield. The result of antimicrobial activity reveals that 4-amino-2-methyl-6-(methylthio)pyrimidine-5-carbonitrile can act as template for further development through modification to design more effective antibacterial agent.

Acknowledgments

The authors are grateful to Principal, Yeshwant Mahavidyalaya, Nanded, for providing laboratory facilities, and the Director, Indian Institute of Chemical Technology, Hyderabad, for providing spectra.

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How to cite this article:
S.P. Vartale, B.D. Kalyankar and D.S. Kawale. (2016). A New efficient synthesis of tetra substituted pyrimidines and their antimicrobial activity. Int. J. Curr. Res. Chem. Pharm. Sci. 3(3): 19-24.