Scholars Academic Journal of Pharmacy (SAJP) **ISSN 2320-4206**
Sch. Acad. J. Pharm., 2013; 2(2):130-134

(An International Publisher for Academic and Scientific Resources)
www.saspublisher.com

Research Article

One Pot Synthesis of Pyrido [1,2-*a*]Pyrimidine Derivatives and Screen their Biological Properties

[1]*Vartale S.P, [2]Halikar N.K, [2]Jadhav A.G, [1]Chavan S.B, [3]Patwari S.B.
[1]P.G. Research centre, Department of chemistry, Yeshwant Mahavidyalaya, Nanded (MS)India.
[2]Department of chemistry, Mahatma Gandhi Mahavidyalaya, Ahmedpur, dist. Latur (MS)India.
[3] Department of chemistry, Yeshwant Mahavidyalaya, dist. Nanded (MS)India.

***Corresponding author**
Vartale S.P
Email: spvartale@gmail.com

Abstract: The ethyl 2-cyano-3,3-bis(methylthio)acrylate (1) on treatment with 2-amino pyridine (2) in ethanol and catalytic amount of TEA, gives 3-cyano-7-methyl-4-oxo-2-(methylthio)-*4H*-pyrido[1,2-*a*]pyrimidine(3).The latter were further reacted with selected N-,O-,and C- nucleophiles such as aryl amines, hetryl amines, substituted phenols and compounds containing an active methylene groups.
Keywords: 2-amino 5-methyl pyridine, ethyl 2-cyano-3,3-bis(methylthio)acrylate, TEA, EtOH.

INTRODUCTION

Oxo pyrimidines [1] and their nucleosides derivatives has been the studied of many chemical and biological studies on account of their interesting pharmacological properties. Thus, as part of an current program for the synthesis of fused heterocyclic systems with expected biological properties [2,3]. The biological significance of the pyrimidine derivatives has leaded us to the synthesis of substituted pyrimidine. As pyrimidine is a basic nucleus in DNA & RNA, it has been found to be associated with diverse biological properties [4]. The synthesis of substituted pyrimidine and many detailed reviews have been appeared Pyrimidines and their derivatives are considered to be important for drugs and agricultural chemicals. Pyrimidine derivatives possess several interesting biological activities such as antimicrobial [5], antitumour [6] and antifungal activities [7]. Many Pyrimidine derivatives are used for thyroid drugs and leukemia. In the present report we present the full experimental details and biological evaluation of a novel pyrimido [1,2-*a*] pyrimidine series.

MATERIALS AND METHODS

Melting points were determined in open capillary tubes and are uncorrected. All the chemicals and solvents used were of laboratory grade and solvents were purified by suitable methods. All the reactions monitored by thin layer chromatography which were 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 . (Chemical shift in δ ppm) using TMS as internal standard. Mass spectra were recorded on FT-VC-7070 H Mass spectrometer using the EI technique at 70 ev. All the reaction was carried out under ambient atmosphere. Elemental analysis was performed on a Heraeus CHN-O rapid analyzer.

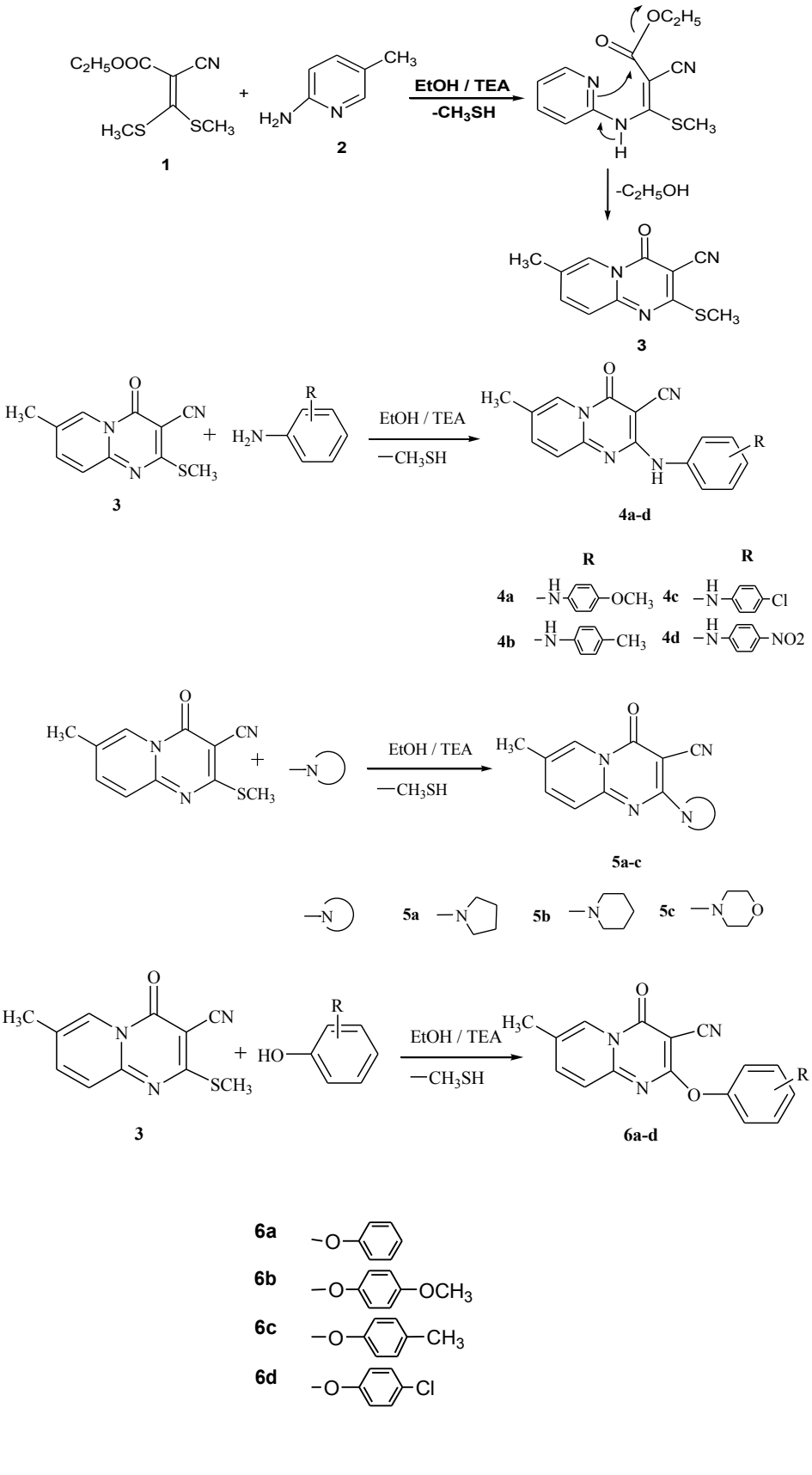
General procedure

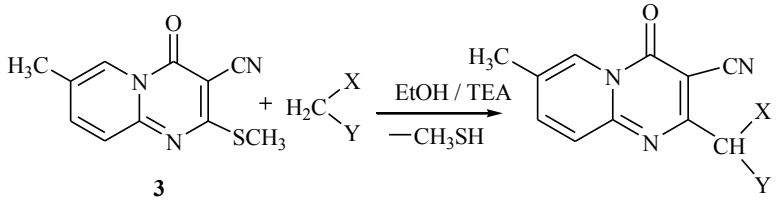
3-Cyano-7-methyl-4-oxo-2-(methylthio)-*4H*-pyrido [1, 2-*a*] pyrimidine (3):

A mixture of 2-amino 5-methyl pyridine **(2)** (0.01 mol) and ethyl 2-cyano-3,3-bis(methylthio) acrylate **(1)** (0.01 mol) in 15 mL of ethanol and catalytic amount of TEA was refluxed for 4 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).**

2-Substituted derivatives of 3-cyano-7-methyl-4-oxo-2-(methylthio)-*4H*-pyrido[1,2-*a*] pyrimidine.(4a-4f, 5a-5d, 6a-d and 7a-d):

A mixture of **3** (0.001 mol) and, independently, various aromatic amines, hetryl amines, substituted phenols or compounds containing an active methylene group (0.001 mol) in ethanol (10 mL) and catalytic amount of TEA was refluxed for 4 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 an N, N'-dimethyl formamide-ethanol mixture to give pure **4a-f, 5a-d, 6a-f** and **7a-d.**


EtOH / TEA
-CH3SH
-C2H5OH
EtOH / TEA
—CH3SH
4a
4b
4c
4d
5a
5b
5c
6a
6b
6c
6d



3 **7a-d**

	X	Y
7a	$-COCH_3$	$-COCH_3$
7b	$-COCH_3$	$-COOC_2H_5$
7c	$-COOC_2H_5$	$-CN$
7d	$-CN$	$-CN$

3-cyano-7-methyl-4-oxo-2-(methylthio)-*4H*-pyrido[1,2-*a*]pyrimidine. (3)
Brown powder, Yield 88 %, M.P 228 °C (dec.). IR (KBr / cm^{-1}) 1648(CO),2210 (CN); ^1H NMR (400 MHz,DMSO-d_6) 2.64 (s, 3H, SCH_3), 7.2-7.4 (d, 2H), 5.1-6.6 (m, 2H),EI-MS (m/z: RA %): 232(M+I).^{13}C NMR (300 MHz, $CDCl_3$) δ:15.5,19.5,87, 116,122,122.6,125,138, 150, 163,170, Anal. Calcd. For: $C_{11}H_9N_3OS$; C, 57.13; H, 3.92; N, 18.17. Found: C, 56.75; H, 3.54; N, 18.07.

3-cyano-7-methyl-4-oxo-2 (4-Methoxy anilino)-*4H*-pyrido[1,2-*a*]pyrimidine (4a).
Brown powder, Yield 82 %, M.P. 221 °C (dec.). IR (KBr/cm^{-1}) 1635(CO),3354 (NH), 2216 (CN). ^1H NMR (400 MHz,DMSO-d_6), 6.1-7.5 (m,8H,Ar-H), 4.1(s,1H,-NH-),3.7(s, 3H, $-OCH_3$), EI MS (m/z: RA %): 306 (M^+), Anal. Calcd. For $C_{17}H_{14}N_4O_2$: C, 66.66; H, 4.61; N, 18.29. Found: C, 66.34; H, 4.41; N, 18.13.

3-cyano-7-methyl -4-oxo-2-(p-methyl anilino)-*4H*-pyrido[1,2-*a*]pyrimidine.(4b)
Brown powder, Yield 78%,M.P.227 °C (dec.). IR (KBr / cm^{-1}) 1631(CO),3348 (NH), 2198 (CN). ^1H NMR (400 MHz, DMSO- d_6) , 6.4-7.7 (m,8H,Ar-H), 4.1(s,1H,-NH-),1.7(s, 3H, Ar-CH_3). EI-MS(m/z:RA%):291(M+I).Anal. Calcd. For $C_{17}H_{14}N_4O$: C, 70.33; H, 4.86; N, 19.30. Found: C, 70.21; H, 4.58; N, 19.18.

3-cyano-7-methyl-4-oxo-2-(4-chloro anilino)-*4H*-pyrido[1,2-*a*]pyrimidine.(4c)
Brown powder, Yield 86 %, M.P 222 °C (dec.). IR (KBr / cm^{-1}) 1625(CO), 3326(NH),2210(CN). EI-MS(m/z:RA%):311(M+I),Anal.Calcd.For:$C_{16}H_{11}ClN_4O$; C, 61.84; H, 3.57; N, 18.03; Found :61.64;H 3.42;N 17.86;

3-cyano-7-methyl-4-oxo-2-(4-nitro anilino) 4H-pyrido[1,2-*a*]pyrimidine.(4d)
Brown powder, Yield 87 %,
M.P. 225 °C (dec.). IR (KBr /cm^{-1}) 1634 (CO), 2217 (CN), 3334 (NH).EI-MS(m/z:RA%):322(M+I),Anal. Calcd. For C16H11N5 O3; C, 59.81; H, 3.45; N, 21.80; Found: 59.64 ; H, 3.25; N, 21.65;

3-cyano-7-methyl-4-oxo-2-(pyrolidino)-*4H*-pyrido[1,2-*a*]pyrimidine(5a)
Brown powder, Yield 74 %, M.P.220 °C (dec.). IR (KBr / cm^{-1}) 1638(CO), 2210(CN), ^1H NMR (400 MHz,DMSO-d_6),1.3(t, 4H,two-CH_2-),2.6(t,4H,two-NCH_2-),5.3-7.5(m,4H,Ar-H)EI-MS(M/Z:RA%)254(M+I), Anal. Calcd. For $C_{14}H_{14}N_4O$; C, 66.13; H, 5.55; N, 22.03; Found : C,66 .02; H,5.27; N,21.87;

3-cyano-7-methyl-4-oxo-2-(piperidino)-4H-pyrido[1,2-*a*]pyrimidine(5b)
Brown powder, Yield 80%, M.P 208 °C (dec.). IR (KBr/ cm^{-1}) 1640(CO), 2214 (CN), EI-MS (M/Z:RA%)268(M^+),Anal. Calcd. For: $C_{15}H_{16}N_4O$; C, 67.15; H, 6.01; N, 20.88; Found: C, 67.02; H, 5.86; N, 20.62;

3-cyano-7-methyl-4-oxo-2-(morpholino) 4H-pyrido[1,2-*a*]pyrimidine.(5c)
Brown powder, Yield 83 %, M.P 214 °C (dec.). IR (KBr / cm^{-1}) 1644(CO), 2222 (CN), EI-MS (M/Z:RA%)271(M+I) Anal. Calcd. For: $C_{14}H_{14}N_4O_2$; C, 62.21; H, 5.22; N, 20.73; Found : C, 62.02; H, 5.04; N, 20.48;

3-cyano-7-methyl-4-oxo-2(phenoxy)4H-pyrido[1,2-*a*]pyrimidine(6a)
Brown powder, Yield 83 %, M.P 223 °C (dec.). IR (KBr / cm^{-1}) 1646(CO), 2208 (CN), EI-MS (m/z: RA %): 278 (M+I), Anal. Calcd. For $C_{16}H_{11}N_3O_3$; C, 69.31; H, 4.00; N, 15.15; Found: C, 69.03;H,3.;N,15.01;

3-cyano-7-methyl-4-oxo-2-(4-methoxyphenoxy) -4H-pyrido[1,2-*a*]pyrimidine.(6b)
Brown powder, Yield 70 %, M.P 202 °C (dec.). IR (KBr / cm^{-1}) 1638(CO), 2198 (CN), ^1H NMR (400 MHz, DMSO- d_6) , 5.5-7.6(m,7H,Ar-H),2.8(s,3H,CH_3),3.5(s,3H,-OCH_3). EI-MS (m/z: RA %): 308 (M+I), Anal. Calcd. For $C_{17}H_{13}N_3O_3$; C, 66.44; H, 4.26; N, 13.67; Found: C, 66.04; H, 4.06; N, 13.47;

3-cyano-7-methyl-4-oxo-2-(p-methyl phenoxy)-4H-pyrido[1,2-*a*]pyrimidine(6c)

Brown powder, Yield 82 %, M.P 225 °C (dec.). IR (KBr / cm^{-1}) 1641(CO),2225 (CN), EI-MS (m/z: RA %): 291 (M+)Anal. Calcd. For $C_{17}H_{13}N_3O_2$; C, 70.09; H, 4.50; N, 14.42;Found: C, 69.78;H,4.23;N,14.13;

3-cyano-7-methyl-4-oxo-2-(4-chloro phenoxy)-4H-pyrido[1,2-*a*]pyrimidine.(6d)
Brown powder, Yield 78%, M.P 229 °C (dec.). IR (KBr / cm^{-1}) 1634(CO), 2219 (CN), EI-MS (m/z: RA %):312 (M+I)Anal. Calcd. For C16H10ClN3O2; C, 61.65; H, 3.23; N, 13.48;Found : C,61.47;H,3.03;N,13.28;

3-cyano-7-methyl-4-oxo-2-(acetyl acetonyl)-4H-pyrido[1,2-*a*]pyrimidine.(7a)
brown powder, Yield 78 %, M.P 241 °C (dec.). IR (KBr / cm^{-1}) 1638(CO), 2216 (CN), EI-MS (m/z: RA %): 284 (M+I),Anal. Calcd. For: $C_{15}H_{13}N_3O_3$, C, 63.60; H, 4.63; N, 14.83 Found: C, 63.21; H, 4.33; N, 14.43;

3-cyano-7-methyl-4-oxo-2-(α-ethyl acetoacetyl)-4H-pyrido[1,2-*a*]pyrimidine.(7b)
Brown powder, Yield 72 %, M.P 234 °C (dec.). IR (KBr / cm^{-1}) 1644(CO), 2221 (CN),EI-MS(m/z:RA%): 313(M+), Anal. Calcd. For $C_{16}H_{15}N_3O_4$; C, 61.34; H, 4.83; N, 13.41; Found: C,61.34;H,4.83;N,13.41;

3-cyano-7-methyl-4-oxo-2-(α-ethyl cyano acetyl)-4H-pyrido[1,2-*a*]pyrimidine.(7c)
Brown powder, Yield 86 %, M.P 230 °C (dec.). IR (KBr / cm^{-1}) 1637(CO), 2212 (CN),EI-MS(m/z:RA%):297(M+I),Anal. Calcd. For : $C_{15}H_{12}N_4O_3$; C, 60.81; H, 4.08; N, 18.91;; Found: C, 60.43; H, 3.88; N, 18.48;

3-cyano-7-methyl-4-oxo-2-(malonyl)-4H-pyrido[1,2-*a*]pyrimidine(7d)
Brown powder, Yield 79 %, M.P 236 °C (dec.). IR (KBr / cm^{-1}) 1646(CO), 2224 (CN), ^{1}H NMR (400 MHz, DMSO- d_6),2.6(s.3H,CH_3)5.1-7.3(m,3H,Ar-H),4.0(s,1H,-CH). EI-MS (m/z: RA %): 249 (M), 224 Anal. Calcd. For $C_{13}H_7N_5O$; C, 62.65; H, 2.83; N, 28.10,Found : C, 62.65; H, 2.83; N, 28.10;

Biological Activity

The antimicrobial activities were determined using disc diffusion [8] method by measuring the zone of inhibition in mm. All newly synthesized compounds **4(a-d) 5 (a-c) 6 (a-d) 7(a-d)** were screened *in vitro* for their antibacterial activity against two Gram-positive strains (*Staphylococcus aureus* and *Bacillus Subtilis)* and two Gram-negative strains *Escherichia coli* at concentration of 500 µg/ml. Antifungal activity was tested against *Candida albicans* and *Aspergillus niger* at concentration of 500 µg/ml. Ciprofloxacin (10 µg/disc) was used as a standard drug for antibacterial screening and Fluconazole (10 µg/disc) was used as a standard for antifungal screening. All newly synthesized compounds exhibited good to moderate antibacterial and antifungal activities.

Table: Antimicrobial activity of compounds 4(a-d) 5 (a-c) 6 (a-d) 7(a-d)

Compound No.	Zone of inhibition in mm				
	Antibacterial activity			Antifungal activity	
	S.aureus	***B.subtilis***	***E.Coli***	***C.albicans***	***A.niger***
4a	10	11	8	12	24
4b	**13**	**15**	**9**	**26**	**12**
4c	10	12	8	19	12
4d	12	13	9	11	12
5a	11	10	9	8	24
5b	10	09	08	22	23
5c	**16**	**18**	**20**	**14**	**20**
6a	13	14	09	17	16
6b	09	16	18	13	10
6c	11	15	17	10	13
6d	16	18	15	13	11
7a	14	16	17	15	16
7b	16	19	08	18	13
7c	**20**	**21**	**23**	**19**	**21**
7d	**21**	**23**	**20**	**21**	**20**
Ciprofloxacin	26	26	28	-	-
Fluconazole	-	-	-	25	25

CONCLUSION

In conclusion, we have described a simple and convenient procedure for the preparation of some novel pyrido [1,2-*a*] pyrimidine derivatives and they possess milder reaction conditions, simple workup, and good yields are the most significant advantages of this new procedure in synthesis of these potential biologically more potent compounds. The elemental and spectroscopy analysis of FTIR, ^{1}H- and ^{13}CNMR were in good agreement with the proposed structure.

ACKNOWLEDGEMENTS

The authors are grateful to Dr. N. V. Kalyankar, Principal, Yeshwant Mahavidyalaya, Nanded, for providing laboratory facilities, To UGC New Delhi for financial assistance under major research project (F.N 39-834/2010 (SR)) and Director, Indian Institute of Chemical Technology, Hyderabad, for providing spectra.

REFERENCES

1. Vartale SP, Halikar NK, Kalyankar ND, Sirsat SB, Pawar YD and Pawde AV; Synthesis of Novel Fused Pyrido Diimino Pyrimido Pyrimido derivatives Incorporating Benzothiazole Compounds, Int.J.of PharmTech Rese., 4(2): 873-877.
2. Ghoneim K M and Youssef R; J Indian Chem Soc, 1986; 53: 914.
3. Kenner GW and Todd A; Heterocyclic Compounds, Ed. R C Elderfield, Wiley, New York, 1957: 6.
4. Brown DJ; The Chemistry of Heterocyclic Compounds, Ed. A. Weissberger, Interscience, New York, 1962; 16.
5. Karale BK and Gill CH; Phenylpyrazolin - 5(4H)-ones and their conversion into 2-thio-5-hydroxy-5H-[1]-benzo- pyrano [4, 3-d] pyrimidines, Indian J Chem, 2002; 41B, 1957.
6. Reddy VM and Sarma Rama GVS; Indian J Heterocycl Chem, Synthesis of 1,2 disubstituted-4-[(chromon-3-yl) methylene]imidazolin-5(4H)-ones as potential pharmacological agents.1993; 3:111.
7. Shingare MS, Karale BK, Gill CH, Gange KN and Bachute MT; Indian J. Heterocycl Chem, 1999; 9: 153.
8. Ananthanarayan R & Panikar JCK, Textbook of Microbiology, Orient Longman, 1999: 578.