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Synthesis and antimicrobial activity of 3-cyano-4-imino-2-(methylthio)-7-methyl-4*H*-pyrido [1,2-*a*] pyrimidine derivatives

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ABSTRACT

*The bis (methylthio) methylene malononitrile **1** on treatment with 2-amino 5-methyl pyridine **2** in N,N'-dimethyl formamide (DMF) and anhydrous potassium carbonate gives 3-cyano-4-imino-2-(methylthio)-7-methyl-4H-pyrido [1,2- a]pyrimidine **3**.The latter were further reacted with selected N-, O- and C- nucleophiles such as aryl amines , heteryl amines, substituted phenols and compounds with an active methylene group.*

Keywords: 2-amino 5-methyl pyridine, bis (methylthio) methylene malononitrile, DMF.

INTRODUCTION

Several type of pyrido [1,2-*a*] pyrimidine have aroused much interest due to their valuable pharmacological properties. Antihypertensive[1], Hypoglycemic[2], Antibacterial[3], Antimalarial[4-5], effects have been observed in a number of pyrido[1,2-*a*] pyrimidines. They are also used as synthetic intermediates or as additives to photographic materials and dyes.The development of physiologically highly potent fused pyrimidine with interesting antiviral, antibacterial, antimalarial , antiallergic, antihypertensive agent and especially anticancer agent[6-9], these valid observation generated us to great interest in facile and general routes to these molecules in synthetic useful yields. In the present note we report that synthesis of 3-cyano-4-imino-2-(methylthio)-7-methyl-4H-pyrido [1,2- *a*]pyrimidine and their substituted derivatives.

EXPERIMENTAL SECTION

Melting point were determined by open capillary tubes and were uncorrected. 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 . 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)-7-methyl-4*H*-pyrido [1,2-*a*]pyrimidine (3)

A mixture of 2-amino 5-methyl pyridine **(2)** (0.01 mol) and bis (methylthio) methylene malononitrile **(1)** (0.01 mol) in 20 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).**

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

A mixture of **(3)** (0.001 m mol) when reacted independently with various aromatic amines , heteryl amines, substituted phenols or compounds containing an active methylene group (0.001 m mol) in N, N'- dimethyl formamide (15 mL) and anhydrous potassium carbonate (10mg) was refluxed for 4 to 6 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 a N, N'- dimethyl formamide-ethanol mixture to give pure **4a-f, 5a-d, 6a-d** and **7a-d.**

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

Orange powder, yield 85 %, m.p. 179 °C (dec.). IR (KBr / cm^{-1}) 3342 (=NH), 2212 (CN); ^{1}H NMR (400 MHz,DMSO-d_6, ppm) , δ 2.1 (s , 3H, Ar-CH_3), 2.6 (s, 3H, SCH_3), 5.4-6.4 (m,3H, HC=C), 5.7-6.3 (m, 3H), 8.9 (br s, 1H, =NH), EI-MS (m/z: RA %): 230(M^+) , 100% , ^{13}C NMR (300 MHz $CDCl_3$) δ 16, 19.5, 79, 116, 120, 122, 137, 138,150,164,165; Anal.Calcd. M.F. $C_{11}H_{10}N_4S$; C, 57.30; H, 4.38; N, 24.33; Found: C, 57.01; H, 4.03; N, 24.02.

3-Cyano-4-imino -2-(p-Methoxy aniline)-7-methyl-4*H*-pyrido[1,2-*a*]pyrimidine (4a).

Brown powder, yield 84%, m.p.212 °C (dec.).IR (KBr / cm^{-1}) 3362 (=NH), 2217 (CN). ^{1}H NMR (400 MHz, DMSO-d_6, ppm), δ 2.3 (s, 3H, Ar-CH_3), 3.7(s, 3H, Ar-OCH_3), 4.2 (s,1H,-NH), 5.6-6.6 (m, 7H,Ar-H), 9.2 (br s, 1H, =NH), EI-MS (m/z: RA %): 305;Anal. Calcd. For C_{17} H_{15} N_5 O; C, 66.87; H, 4.95; N, 22.94, Found: C, 66.24; H, 4.48; N, 22.57,

3-Cyano-4-imino -2-(p-methyl aniline)-7-methyl -4*H*-pyrido[1,2-*a*]pyrimidine(4b).

Brown powder, yield 78**%**, m.p. 218 °C (dec.). IR (KBr / cm^{-1}) 3372 (=NH), 2213 (CN). ^{1}H NMR (400 MHz,DMSO-d_6,ppm), 2.4 (s , 6H, Ar-CH_3), 4.1 (s, 1H,-NH), 5.5-6.9 (m, 7H,Ar-H), 9.2 (br s, 1H, =NH), EI-MS (m/z: RA %): 289 (M^+),Anal. Calcd. For $C_{17}H_{15}N_5$; C, 70.57; H, 5.23; N, 24.21; Found: C, 70.21; H, 5.01; N, 24.05.

3-Cyano-4-imino-2-(m-methoxy aniline)-7-methyl-4*H*-pyrido[1,2-*a*]pyrimidine(4c).

Brown powder, yield 69 %, m.p. 210 °C (dec.). IR (KBr / cm^{-1}) 3378 (=NH), 2218 (CN), Anal. Calcd. For $C_{17}H_{15}N_5O$; C, 66.87; H, 4.95, N, 22.94 Found : C, 66.27; H, 4.46, N, 22.58;

3-Cyano-4-imino-2-(p-chloro aniline)-7-methyl-4*H*-pyrido[1,2-*a*]pyrimidine(4d).

Brown powder, yield 72 %, m.p. 216 °C (dec.). IR (KBr / cm^{-1}) 3389 (=NH), 2197 (CN), EI-MS (m/z: RA %): 309 (M^+) Anal. Calcd. For $C_{16}H_{12}Cl$ N_5; C, 60.04; H, 3.90, N 22.61 Found : C, 59.62; H, 3.46, N 22.31

3-Cyano-4-imino-2-(p-nitro aniline)-7methyl-4*H*-pyrido[1,2-*a*]pyrimidine (4e).

Brown powder, yield 77%, m.p. 223 °C (dec.). IR (KBr / cm^{-1}) 3387 (=NH), 2196 (CN), Anal. Calcd. For $C_{16}H_{12}$ N_6O_2; C, 60.00; H, 3.78; N, 26.24; Found:C, 59.60; H, 3.48; N, 26.01.

3-Cyano-4-imino-2-(o,p-dichloro aniline)-7-methyl-4*H*-pyrido[1,2-*a*]pyrimidine(4f).

Brown powder, yield 87%, m.p 208 °C (dec.). IR (KBr / cm^{-1}) 3377 (=NH), 2210 (CN). Anal. Calcd. For $C_{16}H_{11}Cl_2N_5$; C, 55.83; H, 3.22, N, 20.35; Found : C, 55.62; H, 3.02, N, 20.01;

3-Cyano-4-imino-2-(pyrrolidino)-7-methyl-4*H*-pyrido[1,2-*a*]pyrimidine(5a).

Brown powder, yield 82 %, m.p. 199 °C (dec.). IR (KBr / cm^{-1}) 3380 (=NH), 2219 (CN), ^{1}H NMR (400 MHz,DMSO-d_6,ppm), δ: 1.7(t, 4H,two-CH2-),2.5(t,4H, two-NCH2-),2.8 (s , 3H, Ar-CH_3), 5.4-7.1 (m,4H,Ar-H), 8.9(br s, 1H, =NH), EI-MS (M/Z : RA %): 253(100 %), Anal. Calcd. For $C_{14}H_{15}N_5$; Found : C, 66.38; H, 5.97; N, 27.65;

3-Cyano-4-imino-2-(piperidino)-7-methyl-4*H*-pyrido[1,2-*a*]pyrimidine(5b).

Brown powder, yield 84 %, m.p. 194 °C (dec.). IR (KBr / cm^{-1}) 3376 (=NH), 2216 (CN), EI-MS (M/Z : RA %) 267 Anal. Calcd. For $C_{15}H_{17}N_5$; C, 67.39; H, 6.41; N, 26.20 ;Found :C, 67.01; H, 6.05; N, 26.01

3-Cyano-4-imino-2-morpholino-7-methyl-4*H*-pyrido[1,2-*a*]pyrimidine(5c).

Brown powder, yield 79 %, m.p. 221 °C (dec.). IR (KBr / cm^{-1}) 3374 (=NH), 2196 (CN),), EI-MS (M/Z : RA %) 269 Anal. Calcd. For $C_{14}H_{15}N_5O$; C, 62.22; H, 5.61; N, 26.01; Found : C, 62.02; H, 5.05; N, 25.54;

3-Cyano-4-imino-2-(piperazino)-7-methyl-4*H*-pyrido[1,2-*a*]pyrimidine(5d).
Brown powder, yield 83 %, mp 218 °C (dec.). IR (KBr / cm^{-1}) 3382 (=NH), 2198 (CN), EI-MS (M/Z : RA %) 268; Anal. Calcd. For $C_{14}H_{16}N_6$; C, 62.67; H, 6.01; N, 31.32;Found: C, 62.25; H, 5.57; N, 31.02;

3-Cyano-4-imino-2-(p-methoxyphenoxy)-7-methyl-4*H*-pyrido[1,2-*a*]pyrimidine(6a).
Brown powder, yield 78 %, m.p. 225 °C(dec.). IR (KBr / cm^{-1}) 3385 (=NH), 2221 (CN), ^{1}H NMR (400 MHz,DMSO-d_6,ppm), δ 2.3 (s , 3H, Ar-CH_3), 3.6 (s , 3H, Ar-OCH_3), 5.6-7.2 (m, 7H), 8.9 (br s, 1H, =NH), EI-MS (m/z: RA %): 306, Anal. Calcd. For $C_{17}H_{14}N_4O_2$; C, 66.66; H, 4.61; N, 18.29;Found: C, 66.16; H, 4.21; N, 18.01;

3-Cyano-4-imino-2-(p-tolyloxy)-7-methyl-4*H*-pyrido[1,2-*a*]pyrimidine(6b).
Brown powder, yield 62%, m.p 209 °C (dec.). IR (KBr /cm^{-1}) 3379(=NH), 2226 (CN), EI-MS (m/z: RA %): 290 (M^+).Anal. Calcd. For: $C_{17}H_{14}N_4O$; C, 70.33; H, 4.86; N, 19.30; Found: C, 70.02; H, 4.46; N, 19.03;

3-Cyano-4-imino-2-(p-chlorophenoxy)-7-methyl-4*H*-pyrido[1,2-*a*]pyrimidine(6c).
Brown powder, Brown powder, yield 74 %, m.p. 228 °C (dec.). IR (KBr /cm^{-1}) 3375 (=NH), 2218(CN), EI-MS (m/z: RA %): 310. Anal. Calcd. For $C_{16}H_{11}Cl\ N_4O$; C, 61.84; H, 3.57; N, 18.03; Found: C, 61.54; H, 3.24; N, 17.43;

3-Cyano-4-imino-2-(phenoxy)-7-methyl-4*H*-pyrido[1,2-*a*]pyrimidine (6d).
Brown powder, yield 69 %, m.p. 219 °C (dec.). IR (KBr / cm^{-1}) 3385 (=NH), 2228 (CN), A EI-MS (m/z: RA %): 276 nal. Calcd. For $C_{16}H_{12}N_4O$; C, 69.55; H, 4.38; N, 20.28, Found : C, 69.05; H, 4.03; N, 20.02;

3-Cyano-4-imino-2-(acetyl acetonyl)-7-methyl-4*H*-pyrido[1,2-*a*]pyrimidine (7a).
Brown powder, yield 68 %, m.p. 221 °C (dec.). IR (KBr /cm^{-1}) 3389 (=NH), 2218 (CN), ^{1}H NMR (400 MHz,DMSO-d_6,ppm), δ 1.9 (s , 9H, Ar-CH_3), 2.3 (s , 6H, two,-CO-CH_3), 4.3 (s, 1H,-CH), 5.6-6.7 (m, 3H, Ar-H), 9.3 (br s, 1H, =NH). EI-MS (m/z: RA %): 282.Anal. Calcd. For $C_{15}H_{14}N_4O_2$; C, 63.82; H, 5.00; N, 19.85; Found : C, 63.54; H, 4.62; N, 19.43.

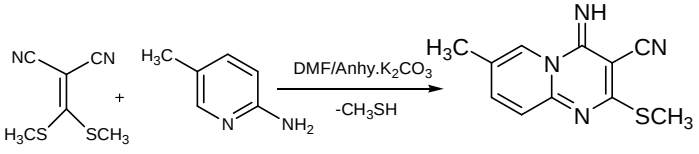
3-Cyano-4-imino-2-(α-ethyl aceto acetyl)-7-methyl-4*H*-pyrido[1,2-*a*]pyrimidine (7b).
Brown powder, yield 66 %, m.p. 218 °C (dec.). IR (KBr /cm^{-1}) 3378 (=NH), 2228 (CN), Anal. Calcd. For $C_{16}H_{16}N_4O_3$;Found : C, 61.53; H, 5.16; N, 17.94;

3-Cyano-4-imino-2-(α-ethyl cyano acetyl)-7-methyl-4*H*-pyrido[1,2-*a*]pyrimidine (7c).
Brown powder, yield 82 %, m.p. 226 °C (dec.). IR (KBr /cm^{-1}) 3382 (=NH), 2222 (CN), Anal. Calcd. For $C_{15}H_{13}N_5O_2$; C, 61.01; H, 4.44; N, 23.72; Found : C, 60.43; H, 4.01; N, 23.41;

3-Cyano-4-imino-2-(malonyl)-7-methyl-4*H*-pyrido[1,2-*a*]pyrimidine (7d).
Brown powder, yield 78 %, m.p. 226 °C (dec.). IR (KBr /cm^{-1}) 3388 (=NH), 2196 (CN), EI-MS (m/z: RA %): 248 Anal. Calcd. For $C_{13}H_8N_6$; C, 62.90; H, 3.25; N, 33.85; Found : C, 62.43; H, 3.01; N, 33.38.

RESULTS AND DISCUSSION

In this present communication synthesized Compound **(3)** were prepared from the reaction of bis (methylthio) methylene malanonitrile **(1)** with 2 –amino 5-methyl pyridine **(2)** in presence of catalytic amount of anhydrous potassium carbonate in N,N'–Dimethyl formamide **(Scheme-I)** . The yield of compound **(3)** is 84 % the structure of this newly synthesized compound with M.P. 179 ^{0}C was confirmed on the basis of elemental analysis IR,^{1}H NMR, ^{13}C NMR and MASS spectral data spectral studies of these compounds are stable and do not exhibit any tautomerism.



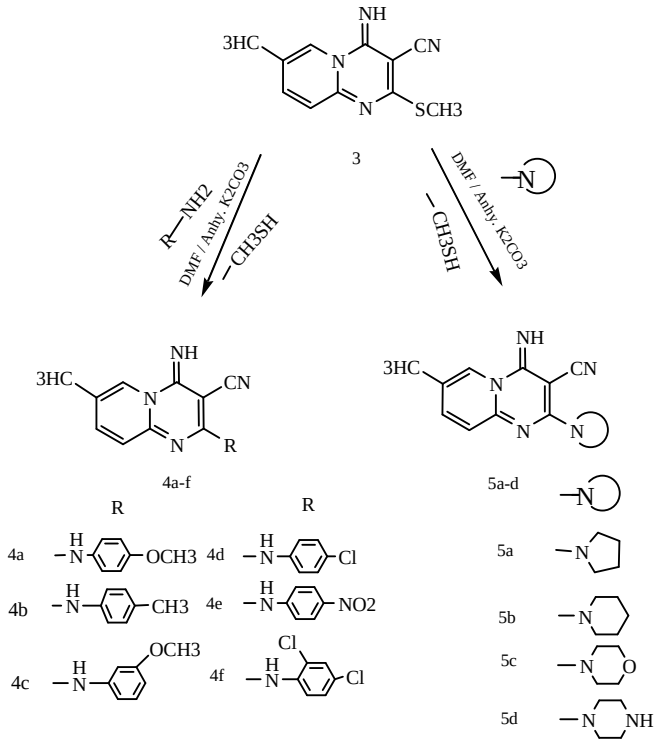
1 **2** **3**

Compound **(3)** posses a replacable active methylthio group at 2- position which is activated by ring 1-nitrogen atom and electron withdrawing group 3-cyano group . compound **(3)** reacted with selected N-,O-, C- nucleophiles like

aryl amines, heteryl amines, substituted phenols and compounds containing an active methylene group. The compound **(3)** on reaction with p-methoxy aniline, p-methyl aniline , o-methyl aniline , p-chloro aniline, p-nitro aniline , o-,p-dimethyl aniline in N,N'-dimethyl formamide and catalytic amount of anhydrous potassium carbonate to afforded 3-cyano-4-imino-2-(4-methoxy aniline/4-methyl aniline / 4-nitro aniline / 3-methoxy aniline /2,4-dichloro aniline)-7-methyl-4*H*-pyrido-[1,2-*b*]pyrimidine **(4a-f)** respectively **(scheme 2) .**

Under similar experimental condition compound **(3)** reacted with heteryl amines like pyrolidine, piperidine, morpholine and piperazine to yielded 3-cyano-4-imino-2(pyrolidino /piperidino / morpholino/piperazino)-7-meyhyl -4*H*-pyrido [1,2-*b*] pyrimidine **(5a-d)** respectively **(scheme 2)** .

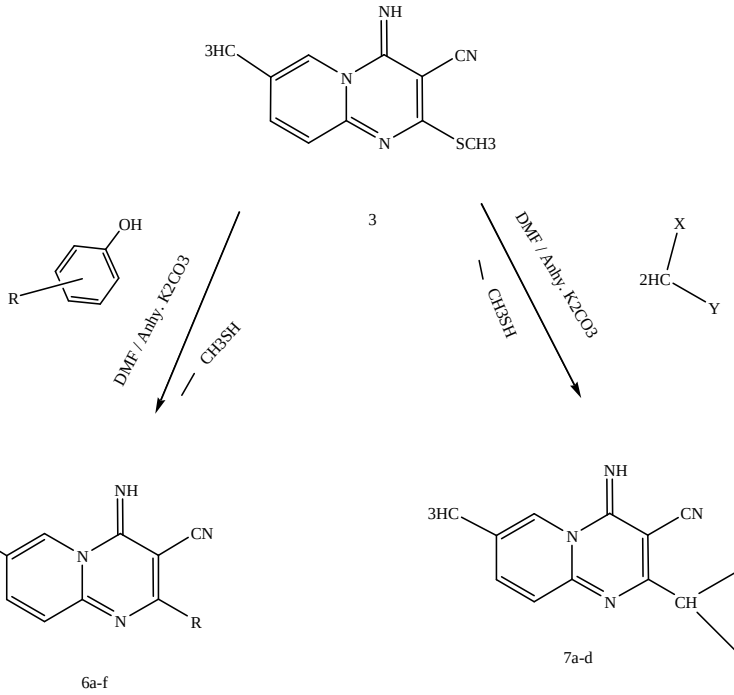
Under similar experimental condition compound **(3)** reacted independently with different substituted phenols in N,N'-dimethyl formamide and catalytic amount of anhydrous potassium carbonate, afforded 3-cyano-4-imino-2-(4-methoxyphenoxy/4-tolyoxy/ 4-chlorophenoxy/ phenoxy) -7-methyl-4*H*-pyrido[1,2-*b*] pyrimidine **(6a-d) (scheme-3).**



Scheme-2

And also under similar experimental condition compound **(3)** reacted independently with different substituted active methylene group like acetyl acetone ,ethyl acetoacetate **,**ethyl cyano acetate, malanonitrile in presence of N,N'-dimethyl formamide and catalytic amount of anhydrous potassium carbonate to afforded 3-cyano-4-imino -2-(acetyl acetonyl/α-ethyl acetoacetonyl / α-ethyl cyano acetonyl /malonyl) -7-methyl-4*H*-pyrido[1,2-*b*] pyrimidine **(7a-d)** respectively.

All these newly synthesized compound 4a-g , 5a-d , 6a-f and 7a-d show absorption bands in their IR spectra in the range of 3350 cm^{-1} to 3450 cm^{-1} and 2190cm^{-1} to 2230cm^{-1} due to =NH and –CN stretching. Respectively ^1H – NMR and mass spectral data are also in agreement with structures assigned to compounds **4a-g, 5a-d,6a-f and 7a-d.**



R

6a —O—OCH_3

6b —O—CH_3

6c —O—Cl

6d —O—

Scheme-3

	X	**Y**
7a	—$COCH_3$	—$COCH_3$
7b	—$COOC_2H_5$	—$COOC_2H_5$
7c	—$COOC_2H_5$	—CN
7d	—CN	—CN

Antimicrobial activity

The synthesized compounds were evaluated 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[10]. All the synthesized compounds were dissolved in dimethyl sulphoxide. The synthesized compounds exhibited zone of inhibition of 09-13 mm in diameter where as standard

Streptomycin exhibited zone of inhibition of 18 and 22 mm in diameter against *S. aureus* and *B. substilis* and Penicillin exhibited zone of inhibition of 15 and 16 mm in diameter against *E. coli* and *S. typhi* respectively. Amongst the synthesized compounds **3,** compound **4e** , **5c, 6c, 7d** showed higher zone of inhibition against *S. aureus, B. substilis, E. coli* and *S. typhi* respectively. It seems that the presence of -NO_2 , -Cl and -CN group at 2-position **4e, 5c, 6c, 7d** increases antibacterial activity.

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