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

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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, hetero 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 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 (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, hetero 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.
3-cyano-7-methyl-4-oxo-2-(methylthio)-1H-pyrido[1,2-α]pyrimidine. (3)
Brown powder, Yield 88 %, M.P 228 °C (dec.). IR (KBr / cm⁻¹ ) 1648(CO),2210 (CN); ¹H NMR (400 MHz,DMSO-d₆) 2.64 (s, 3H, SCH₃ ), 7.2-7.4 (d, 2H), 5.1-6.6 (m, 2H).EI-MS (m/z: RA %): 232(M+H),¹C NMR (300 MHz, CDCl₃) 6:1.5,19,5,87, 116,122,126,125,138, 150, 163,170. Anal. Calcd. For: C₁₅H₁₅N₂O₃; C, 56.75; H, 3.54; N, 18.07.

3-cyano-7-methyl-4-oxo-2-(4-methoxy anilino)-1H-pyrido[1,2-α]pyrimidine(4a).
Brown powder, Yield 82 %, M.P 221 °C (dec.). IR (KBr/cm⁻¹ ) 1635(CO),3348 (NH), 2216 (CN). ¹H NMR (400 MHz,DMSO-d₆), 6.1-7.5 (m,8H,Ar-H), 4.1(s,1H,-NH-), 3.7(s, 3H, -OCH₃), EI MS (m/z: RA %): 306 (M⁺), Anal. Calcd. For: C₁₇H₁₅N₂O₃, C, 66.34; H, 4.41; N, 18.13.

3-cyano-7-methyl -4-oxo-2-(p-methyl anilino)-1H-pyrido[1,2-α]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- d₆), 6.4-7.7 (m,8H,Ar-H), 4.1(s,1H,-NH-), 7.5(s, 3H, -OCH₃), EI-MS(m/z:RA%):291(M⁺).Anal. Calcd. For: C₁₇H₁₅N₂O₃, 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)-1H-pyrido[1,2-α]pyrimidine(4c)
Brown powder, Yield 86 %, M.P 222 °C (dec.). IR (KBr / cm⁻¹ ) 1625(CO), 1635(CO),3348(NH), 3236(NH),2210(CN). EI-MS(m/z:RA%):311(M⁺),Anal.Calcd.For:C₁₈H₁₃ClN₂O₂, 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-α]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⁺),Anal. Calcd. For C₁₆H₁₁N₅O₃; 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-(p-methyl anilino)-1H-pyrido[1,2-α]pyrimidine(4e).
Brown powder, Yield 74 %, M.P 220 °C (dec.). IR (KBr / cm⁻¹ ) 1638(CO), 2210(CN), ¹H NMR (400 MHz, DMSO- d₆), 5.5-7.6(m,7H,Ar-H),2.8(s,3H,CH₃),3.5(s,3H,-OCH₃). EI-MS (m/z: RA %): 308 (M⁺), Anal. Calcd. For: C₁₇H₁₅N₂O₃, 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-(methylthio)-1H-pyrido[1,2-α]pyrimidine(5a).
Brown powder, Yield 74 %, M.P 220 °C (dec.). IR (KBr / cm⁻¹ ) 1638(CO), 2210(CN), ¹H NMR (400 MHz, DMSO-d₆), 1.3(t, 4H,two-CH₂-), 2.6(t,4H,two-NCH₂-), 5.3-7.5(m,4H,Ar-H)EI-MS(M/Z:RA%)254(M⁺), Anal. Calcd. For: C₁₇H₁₅N₂O₃, 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)-1H-pyrido[1,2-α]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: C₁₇H₁₅N₂O₃, 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-(morpholinol) 4H-pyrido[1,2-α]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⁺), Anal. Calcd. For: C₁₇H₁₅N₂O₃, 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-α]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⁺), Anal. Calcd. For: C₁₈H₁₅N₂O₃, 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-α]pyrimidine.(6b).
Brown powder, Yield 70 %, M.P 202 °C (dec.). IR (KBr / cm⁻¹ ) 1638(CO), 2198 (CN), ¹H NMR (400 MHz, DMSO- d₆), 5.5-7.6(m,7H,Ar-H),2.8(s,3H,CH₃),3.5(s,3H,-OCH₃). EI-MS (m/z: RA %): 308 (M⁺), Anal. Calcd. For: C₁₇H₁₅N₂O₃, C, 66.44; H, 4.26; N, 13.67; Found: C, 66.04; H, 4.06; N, 13.47;
Brown powder, Yield 82 %, M.P 225 °C (dec.). IR (KBr / cm ) 1614(CO),2225 (CN), EI-MS (m/z: RA %): 291 (M+)Anal. Calcd. For C19H13N2O3; C, 66.50; H, 3.86; N, 14.42; Found: C, 66.78; H, 4.23; N, 14.13;

3-cyano-7-methyl-4-oxo-2-(4-chloro phenoxy)-4H-pyrido[1,2-α]pyrimidine(6d)
Brown powder, Yield 78%, M.P 229 °C (dec.). IR (KBr / cm ) 1634(CO), 2219 (CN), EI-MS (m/z: RA %): 312 (M+)Anal. Calcd. For C16H10ClN3O2; C, 61.09; 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-α]pyrimidine(7a)
Brown powder, Yield 78 %, M.P 241 °C (dec.). IR (KBr / cm ) 1638(CO), 2216 (CN), EI-MS (m/z: RA %): 284 (M+),Anal. Calcd. For C15H13N2O2; 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 acetocacetyl)-4H-pyrido[1,2-α]pyrimidine(7b)
Brown powder, Yield 72 %, M.P 234 °C (dec.). IR (KBr / cm ) 1644(CO), 2221 (CN), EI-MS (m/z: RA %): 313(M), Anal. Calcd. For C13H13N2O2; C, 63.14; H, 4.83; N, 13.41; Found: C, 63.34; H, 4.83; N, 13.41;

3-cyano-7-methyl-4-oxo-2-(α-ethyl cyano acetyl)-4H-pyrido[1,2-α]pyrimidine(7c)
Brown powder, Yield 86 %, M.P 230 °C (dec.). IR (KBr / cm ) 1637(CO), 2212 (CN), EI-MS (m/z: RA %): 297 (M+1), Anal. Calcd. For C13H12N2O3; 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-α]pyrimidine(7d)
Brown powder, Yield 79 %, M.P 236 °C (dec.). IR (KBr / cm ) 1646(CO), 2224 (CN), 1H NMR (400 MHz, DMSO-d6): 2.6(s,3H,CH3), 5.1-7.3(m,3H,Ar-H), 4.0(s,1H,-CH). EI-MS (m/z: RA %): 249 (M), 224 Anal. Calcd. For C10H12N2O; 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.** | **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-α] 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, ¹H- and ¹³C-NMR were in good agreement with the proposed structure.
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