SYNTHESIS WITH NITRILES: 92[1]. SYNTHESIS OF 5-FORMYLCYTOSINE DERIVATIVES

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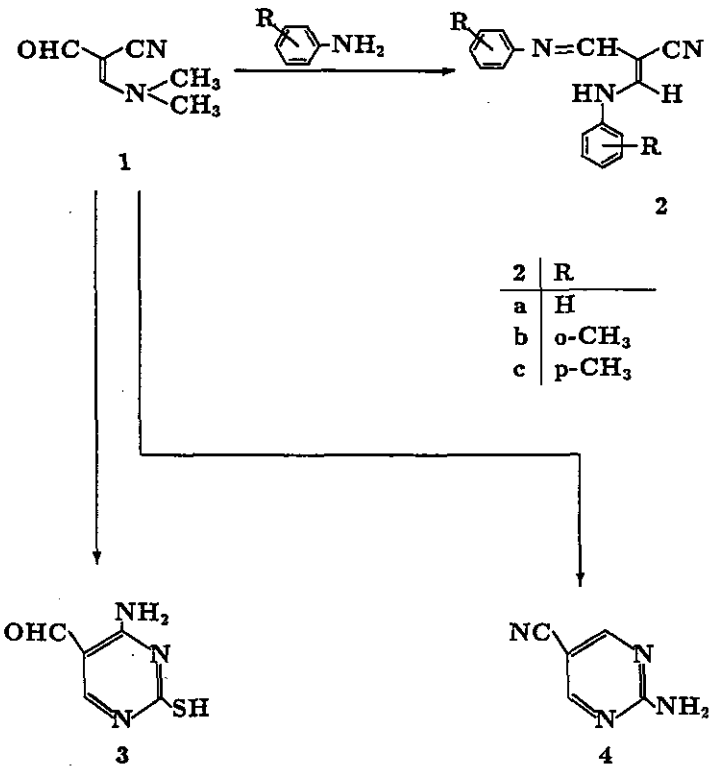
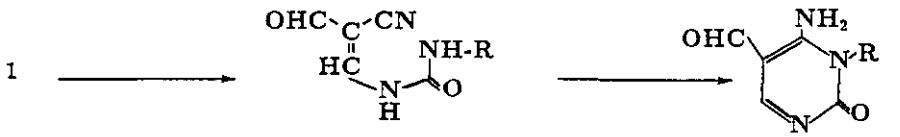
Abstract- The reactivity of 3-dimethylamino-2-formylpropenenitrile **(1)** with various amino compounds is studied. Thus, condensation of **1** with anilines gives the corresponding azomethines **(2a-c)**. Reaction of **1** with thiourea and guanidine resp., leads to 5-formylthiocytosine **(3)** and 2-amino-5-cyanopyrimidine **(4)**. The 2-formyl-3-ureidopropenenitriles **(5a-i)** can be obtained by reaction of **1** with urea and substituted ureas. **5a-i** can easily be cyclized to 3-substituted 5-formylcytosines **(6a-e)**. Condensation of **6** with aniline, benzylamine and phenylhydrazine leads to the azomethines **(7a-i)**. Pyrido [2,3-*d*] pyrimidine-6-carbonitriles **(8a, 8b, 8d and 8e)** are obtained by reaction of **6** with malononitrile.

Recently we have described a new route for the synthesis of 3-dimethylamino-2-formylpropenenitrile **(1)**, which can be obtained by condensation of freshly prepared cyanoacetaldehyde with dimethylformamide dimethylacetal.[1,2] **1** is a useful starting material for various heterocycles, especially pyrazoles and pyrimidine derivatives.[3-5] In this paper we want to describe the synthesis of 2(1*H*)pyrimidinones and 3-substituted 5-formylcytosine derivatives. 2(1*H*)pyrimidinones are of considerable interest because of the biological activities exhibited by many of these compounds.[6,7] For instance cytosine nucleosides have proven to be most effective therapeutic agents for treatment of aquired immune deficiency syndrom (AIDS)[8] and recently cytosine has been used for the synthesis of acyclic nucleic acid analogues, which have the capability of binding in a sequence specific manner to DNA and RNA.[9] Compound **(1)** reacts with two moles of aniline and toluidines to give the 3-arylimino-1-arylaminopropene-2-carbonitriles **(2a-c)**. **2a** was also obtained by reaction of cyanomalonodialdehyde and aniline.[10,11]

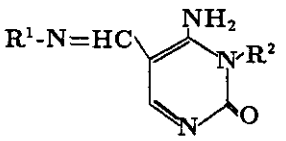


Thiourea and guanidine react with **1** under alkaline conditions to give the hitherto not described 5-formylthiocytosine **(3)** and 2-amino-5-cyanopyrimidine **(4)**. Compound **(4)** was first prepared by English *et al.*[12] by reaction of 2-amino-5-bromopyrimidine with cuprous cyanide. **4** can also be obtained by reaction of 2-chloro-5-cyanopyrimidine with ammonia.[13] Reaction of **1** with urea and *N*-substituted ureas under acidic conditions, however, leads to the openchained derivatives **(5a-i)**, which can be cyclized by heating in acetonitrile with triethylamine to give the 5-formyl-cytosine derivatives **(6a-e)**. This ring closure reaction could not be performed with the derivatives **(5f-i)**.

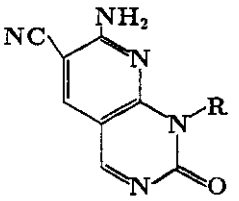


5 a-i

6 a-e



7 a-i



8a-b, d-e

5,6,8	R
a	-CH_3
b	-C_2H_5
c	-C_6H_5
d	-CH_2-C_6H_5
e	-CH_2-CH=CH_2
f	-H
g	-4-Cl-C_6H_4
h	-2-F-C_6H_4
i	-2-CF_3-C_6H_4

7	R^1	R^2
a	-C_6H_5	-CH_3
b	-C_6H_5	-C_2H_5
c	-C_6H_5	-CH_2-C_6H_5
d	-C_6H_5	-CH_2-CH=CH_2
e	-CH_2-C_6H_5	-C_2H_5
f	-NH-C_6H_5	-C_2H_5
g	-4-CH_3-C_6H_4	-C_2H_5
h	-4-Cl-C_6H_4	-C_2H_5
i	-CH_2-3-(pyridyl)	-C_2H_5

The structure of **6a-e** was confirmed by ^{1}H-nmr data, elemental analysis as well as further condensation *reactions. Thus, condensation of* ***6*** *with anilines, benzylamine and phenylhydrazine gives the azomethines* **(7a-i)**. Further ring condensation can be performed by reaction of **6a-b** and **6d-e** with malononitrile, which leads to 7-amino-2-oxo-1,2-dihydro-pyrido [2,3-*d*] pyrimidine-6-carbonitriles **(8a-b, d-e)**.

EXPERIMENTAL PART

Melting points were determined on a Tottoli Apparaturs and are uncorrected. Elemental Analysis with a Carlo Erba Elemental Analyzer. Ir spectra were recorded on a Perkin-Elmer 421. ^{1}H and ^{13}C Nmr spectra were obtained on a Varian 200 gemini spectrometer with TMS as an interal standard.

Synthesis of 2a-c: General Procedure

To a solution of **1** (10 mmol) and aniline or substituted anilines (20 mmol) in 25 ml of ethanol, 2 ml of acetic acid as added and the mixture was heated under reflux for 2.5 h. The solvent was removed in vacuo to get the compounds **(2a-c)**, which were recrystallized from ethanol.

3-Phenylimino-1-phenylaminopropene-2-carbonitrile **(2a)**
85 %; mp 128°C [lit.,[11] mp 131-132°C].

3-(2-Methyl)phenylimino-1-(2-methyl)phenylaminopropene-2-carbonitrile **(2b)**
75 %; mp 116° C; ir (KBr): 2220, 1640 cm^{-1}: ^1H nmr (DMSO-d_6) δ : 2.30 (s, 6H, $2CH_3$), 7.10-7.40 (m, 8H, Ar-H), 8.33 (s, 1H, CH=), 8.35 (s, 1H, CH=), 12.60 (s, 1H, NH); Anal. Calcd for $C_{18}H_{17}N_3$: C,78.51; H, 6.21, N, 15.26: Found: C, 78.58; H, 6.17; N, 15.17.

3-(4-Methyl)phenylimino-1-(4-methyl)phenylaminopropene-2-carbonitrile **(2c)**
68 %; mp 143° C; ir (KBr): 3110, 2220 cm^{-1}; No ^1H nmr: substance decomposes in DMSO-d_6. Anal. Calcd for $C_{18}H_{17}N_3$: C, 78.51; H, 6.21; N, 15.26: Found: C, 78.26; H, 6.27; N, 15.22.

5-Formylthiocytosine (3)

To a boiling solution of 2.5 g (20 mmol) of **1** and 1.9 g (25 mmol) of thiourea in 50 ml of methanol, 12.5 ml of 2N-sodiummethoxide was added dropwise during 1 h and the mixture was heated under reflux for 5 h. The solvent was removed in vacuo and the residue obtained was dissovled in 30 ml of water and precipitated with 10 ml of 30 % acetic acid. It was recrystallized from water. 1.98 g (55 %); mp 265° C; ir (KBr): 3380, 2800-3100, 1660, 1640 cm^{-1}; ^1H nmr (DMSO-d_6); δ : 8.10 (s, 1H, SH), 8.37 (s, 1H, Ar-H), 8.60 (br s, 2H, NH_2), 9.60 (s, 1 H, CHO): Anal. Calcd for $C_5H_5N_3OS$: Anal. Calcd for C, 38.90; H, 3.24; N, 27.02: Found C, 39.24; H, 3.21; N, 27.04.

2-Amino-5-cyanopyrimidine (4)

To a solution of 1.25 g (10 mmol) of **1** and 1.08 g (5 mmol) of guanidine sulfate in 25 ml of methanol, 12.5 ml of 2N sodium methoxide was added dropwise and the mixture was heated under reflux for 5 h. The solvent was removed in vacuo, the residue obtained was washed with 10 ml of 30 % acetic acid and then with 30 ml of water. It was recrystallized from ethanol. 0.82 g (64 %); mp 263° C [lit.,[14] mp 264° C].

Synthesis of 2-formyl-3-ureidopropenenitriles (5a-i): General Procedure

To an equimolar solution of **1** (10 mmol) and urea (10 mmol) or *N*-substituted urea in 25 ml of ethanol, 1.2 ml of conc. hydrochloric acid was added and the mixture was heated for the time as shown below. The solvent was removed in vacuo and all the compounds **(5a-i)** were recrystallized from ethanol.

2-Formyl-3-(3-methylureido)propenenitrile **(5a)**

Heating under reflux for 1.5 h.72 %; mp 192° C; ir (KBr): 3350, 3250, 3190, 3040, 2220, 1740, 1660 cm^{-1}; ^1H nmr (DMSO-d_6) δ : 2.78 (d, J=5.0 Hz, CH_3), 7.11 (d, J=5.0 Hz, 1H, NH), 8.60 (s, 1H, CH=), 9.35 (s, 1H, CHO), 10.68 (br s, 1H, NH); Anal. Calcd for $C_5H_7N_3O_2$: C, 47.07; H, 4.60; N, 27.44: Found: C, 46.98; H, 4.52; N, 27.56.

2-Formyl-3-(3-ethylureido)propenenitrile **(5b)**

Heating at 50° C for 3 h. 70 %; mp 153°C; ir (KBr): 3350, 3260, 3040, 2980, 2230, 1730, 1660 cm^{-1}; ^1H nmr (DMSO-d_6) δ : 1.12 (t, J=7.5 Hz, 3H, CH_3), 3.12-3.30 (m, 2H, CH_2), 7.25 (br s, 1H, NH); 8.60 (s, 1H, CH=), 9.38 (s, 1 H, CHO), 10.58 (br s, 1 H, NH), Anal. Calcd for $C_7H_9N_3O_2$: C, 50.28; H, 5.42; N, 25.13: Found: C, 50.24; H, 5.34; N, 25.39.

2-Formyl-3-(3-phenylureido)propenenitrile **(5c)**

Heating under reflux for 2.5 h. 75 %; mp 193° C; ir (KBr): 3340, 3180, 3110, 2940, 2230, 1755, 1660 cm^{-1}; ^1H nmr (DMSO-d_6) δ : 7.10-7.58 (m, 5H, Ar-H), 8.72 (d, J=15 Hz, 1H, CH=), 9.45 (s, 1H, CHO); 9.59 (s, 1H, NH), 10.68 (d, J=15 Hz, 1H, NH); Anal. Calcd for $C_{11}H_9N_3O_2$: C, 61.41; H, 4.21; N, 19.53: Found: C, 61.64; H, 4.16; N, 19.61.

2-Formyl-3-(3-benzylureido)propenenitrile **(5d)**

Heated under reflux for 2h. 65 %; mp 150° C; ir (KBr): 3355, 3250, 3210, 3030, 2940, 2225, 1740, 1655 cm^{-1}; ^1H nmr (DMSO-d_6) δ : 4.40 (d, J=6.5 Hz, 2H, CH_2), 7.20-7.41 (m, 5H, Ar-H), 7.65 (d, J=6.5 Hz, 1H, NH), 8.61 (d, J=12.5 Hz, 1H, CH=), 9.35 (s, 1H, CHO), 10.61 (d, J=12.5 Hz, 1H, NH); Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.90; H, 4.83; N,18.33: Found: C, 62.58; H, 4.95; N, 18.50.

2-Formyl-3-(3-allylureido)propenenitrile **(5e)**

Heating at 50° C for 2.5 h. 58 %; mp 145° C; ir (KBr): 3390, 3270, 3040, 2225, 1720, 1685 cm^{-1}; ^1H nmr (DMSO-d_6) δ : 3.70-3.90 (m, 2H, CH_2), 5.08-5.30 (m, 2H, CH_2=), 5.72-6.00 (m, 1H, CH=), 7.38 (t, J=6.5 Hz, 1H, NH), 8.62 (d, J=12.5 Hz, 1H, CH=), 9.38 (s, 1H, CHO), 10.68 (d, J=12.5 Hz, 1H, NH); Anal. Calcd for $C_8H_9N_3O_2$: C, 53.62; H, 5.06; N, 23.45: Found: C, 53.47; H, 5.13; N, 23.29.

2-Formyl-3-(3-ureido)propenenitrile **(5f)**

Heating under reflux for 3 h. 79 %; mp 189° C; ir (KBr): 3450, 3330, 3190, 3040, 2970, 2238, 1760, 1665 cm^{-1}; ^1H nmr (DMSO-d_6) δ : 6.70 and 7.49 (s, 2H, NH_2), 8.52 (d, J=12.5 Hz, 1H, CH=), 9.35 (s, 1H, CHO), 10.68 (d, J=12.5 Hz, 1H, NH); Anal. Calcd for $C_5H_5N_3O_2$: C, 43.16; H, 3.62; N, 30.19: Found: C, 43.06; H, 3.94; N, 30.20

2-Formyl-3-(3-[4-chlorophenyl] ureido)propenenitrile **(5g)**

Heating at 50° C for 3 h. 70 %; mp 195° C; ir (KBr): 3230, 3190, 2230, 1750, 1665 cm^{-1}; ^1H nmr (DMSO-d_6) δ : 7.38-7.58 (m, 4H, Ar-H), 8.70 (d, J=12.5 Hz, CH=), 9.42 (s, 1H, CHO), 9.68 (s, 1H, NH), 10.62 (d, J=12.5 Hz, 1H, NH); Anal. Calcd for $C_{11}H_8N_3O_2Cl$: C, 52.94; H, 3.23; Cl, 14.16; N, 16.83: Found: C, 52.69; H, 3.31; Cl, 14.12; N, 16.95.

2-Formyl-3-(3-[2-fluorophenyl]ureido)propenenitrile **(5h)**

Heating at 50° C for 2.5 h. 70 %; mp 185° C; ir (KBr): 3340, 3270, 3050, 2235, 1745, 1680 cm^{-1}; ^1H nmr (DMSO-d_6) δ : 7.08-7.38 (m, 3H, Ar-H), 8.10-8.22 (m, 1H, Ar-H), 8.72 (d, J=12.5 Hz, 1H, CH=), 9.45 (s, 1H, CHO), 9.58 (s, 1H, NH), 10.92 (d, J=12.5 Hz, 1H, NH); Anal. Calcd for $C_{11}H_8N_3O_2F$: C, 56.65; H, 3.45; N, 18.01: Found: C, 56.85; H, 3.63; N, 18.29.

2-Formyl-3-(3- [2- trifluoromethylphenyl] ureido)propenenitrile **(5i)**

Heating at 50° C for 3 h. 65 %; mp 193° C; ir (KBr): 3310, 3210, 3110, 3045, 2230, 1750, 1660 cm^{-1}; ^1H nmr (DMSO-d_6) δ : 7.42-7.70 (m, 3H, Ar-H), 7.98 (s, 1H, Ar-H), 8.72 (d, J=12.5 Hz, 1H, CH=), 9.48 (s, 1H, CHO), 9.90 (s, 1H, NH), 10.68 (d, J=12.5 Hz, 1H, NH); Anal. Calcd for $C_{12}H_8N_3O_2F_3$: C, 50.89; H, 2.84; N, 14.92: Found: C, 50.45; H, 3.12; N, 14.92.

4-Amino-2-oxo-2,3-dihydropyrimidine-5-carbaldehydes (6a-e) General Procedure

To a solution of **5a-e** (10 mmol) in 30 ml of acetonitrile, 3 ml (30 mmol) of triethylamine was added and the mixture was heated under reflux for the time shown below. The solvent was removed in vacuo to get **6a-e**, which were recrystallized from ethanol.

4-Amino-3-methyl-2-oxo-2,3-dihydropyrimidine-5-carbaldehyde **(6a)**

Heating under reflux for 12 h. 55 %; mp 230° C, ir (KBr): 3410, 3165, 1675, 1645 cm^{-1},^1H nmr (DMSO-d_6) δ : 3.38 (s, 3H, CH_3), 8.48 (s, 1H, CH=), 8.60 and 9.25 (br s, 2H, NH_2), 9.50 (s, 1 H, CHO); Anal. Calcd for $C_6H_7N_3O_2$: C, 47.05; H, 4.60; N, 27.43: Found: C, 46.91; H, 4.64; N, 27.37.

4-Amino-3-ethyl-2-oxo-2,3-dihydropyrimidine-5-carbaldehyde **(6b)**

Heating under reflux for 15 h. 65 %; mp 240° C; ir (KBr): 3315, 2840, 1690, 1570 cm^{-1}; ^1H nmr (DMSO-d_6) δ : 1.15 (t, J=7.5 Hz, 3H, CH_3), 3.98 (q, J=7.5 Hz, 2H, CH_2), 8.48 (s, 1H, CH=), 8.62 and 9.32 (br s, 2H, NH_2), 9.50 (s, 1 H, CHO); Anal. Calcd for $C_7H_9N_3O_2$: C, 50.28; H, 5.42; N, 25.13: Found: C, 50.46; H, 5.48; N, 25.30.

4-Amino-3-phenyl-2-oxo-2,3-dihydropyrimidine-5-carbaldehyde **(6c)**

Heating under reflux for 6 h. 35 %; mp 264°C; ir (KBr): 3370, 3150, 1690, 1645 cm^{-1}; ^1H nmr (DMSO-d_6) δ : 7.38-7.65 (m, 5H, Ar-H), 8.62 (s, 1H CH=), 9.12 (br s, 1H, NH_2), 9.58 (s, 1H, CHO); Anal. Calcd for $C_{11}H_9N_3O_2$: C, 61.30; H, 4.21; N, 19.53: Found: C, 60.93; H, 4.28; N, 19.34.

4-Amino-3-benzyl-2-oxo-2,3-dihydropyrimidine-5-carbaldehyde **(6d)**

Heating under reflux for 6 h. 60 %; mp 239° C; ir (KBr): 3260, 3120, 1685, 1625 cm^{-1}; ^1H nmr (DMSO-d_6) δ : 5.25 (s, 2H, CH_2), 7.18-7.48 (m, 5H, Ar-H), 8.58 (s, 1H, CH=), 8.90 and 9.42 (br s, 2H, NH_2), 9.55 (s, 1H, CHO); Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.83; N, 18.33: Found: C, 62.86; H, 4.87; N, 18.25.

4-Amino-3-allyl-2-oxo-2,3-dihydropyrimidine-5-carbaldehyde **(6e)**

Heating under reflux for 4 h. 68 %; mp 219° C; ir (KBr): 3490, 3160, 1645, 1565 cm^{-1}; ^1H nmr (DMSO-d_6) δ : 4.58 (d, J=6.5 Hz, 2H, CH_2), 4.98-5.22 (m, 2H, CH_2=), 5.75-5.98 (m, 1H, CH=), 8.48 (s, 1H, CH=), 8.62 and 9.32 (br s, 2H, NH_2), 9.52 (s, 1 H, CHO); Anal. Calcd for $C_3H_9N_3O_2$ C, 53.62; H, 5.06; N, 23.45: Found: C, 53.59; H, 5.11; N, 23.49.

Synthesis of 4-Amino-5-arylmethylenepyrimidin-2(3*H*)-ones (7a-i)

General Procedure

To an equimolar solution (10 mmol) of **6** and aniline (or substituted aniline), benzylamine (or substituted benzylamine) or phenylhydrazine in 75 ml of distilled water, 2 ml of acetic acid was added and the mixture was stirred at 25° C for 20 h. The solid obtained was filtered and washed with 25 ml of water. All compounds **(7a-i)** were recrystallized from ethanol.

4-Amino-3-methyl-5-phenylaminomethylenepyrimidin-2(3*H*)-one **(7a)**

65 %; mp 270° C; ir (KBr): 2960, 1670, 1610, 1570 cm^{-1}; ^1H nmr (DMSO-d_6) δ : 3.38 (s, 3H, CH_3), 7.19-7.46 (m, 5H, Ar-H), 8.35 (s, 1H, CH=), 8.56 (s, 1H, CH=), 8.55 and 10.50 (br s, 2H, NH_2); Anal. Calcd for $C_{12}H_{12}N_4O$: C, 63.04; H, 5.19; N, 24.52: Found: C, 62.79; H, 5.13; N, 24.61.

4-Amino-3-ethyl-5-phenylaminomethylenepyrimidin-2(3*H*)-one **(7b)**

75 %; mp 246° C; ir (KBr): 2980, 1685, 1615, 1575 cm^{-1}; ^1H nmr (DMSO-d_6) δ : 1.20 (t, J=6.5 Hz, 3H, CH_3), 4.02 (q, J=6.5 Hz, 2H, CH_2), 7.16-7.49 (m, 5H, Ar-H), 8.30 (s, 1H, CH=), 8.56 (s, 1H, CH=), 8.75 and 10.58 (br s, 2H, NH_2); Anal. Calcd for $C_{13}H_{14}N_4O$: C, 64.44; H, 5.82; N, 23.12: Found: C, 64.24; H, 5.71; H, 22.92.

4-Amino-3-benzyl-5-phenylaminomethylenepyrimidin-2(3*H*)-one **(7c)**

62 %; mp 203° C; ir (KBr): 3040, 1665, 1610, 1575 cm^{-1}; ^1H nmr (DMSO-d_6) δ : 5.28 (s, 2H, CH_2), 7.16-7.47 (m, 10H, Ar-H), 8.41 (s, 1H, CH=), 8.61 (s, 1H, CH=), 8.82 and 10.70 (br s, 2H, NH_2); Anal. Calcd for $C_{18}H_{16}NO$: C, 71.02; H, 5.30; N, 18.41: Found: C, 68.02; H, 5.07; N, 18.30.

4-Amino-3-allyl-5-phenylaminomethylenepyrimidin-2(3*H*)-one **(7d)**

64 %; mp 227° C; ir (KBr): 3020, 1670, 1615, 1575 cm^{-1}; ^1H nmr (DMSO-d_6) δ : 4.64 (d, J=4.5 Hz, 2H, CH_2), 5.05-5.23 (m, 2H, CH_2=), 5.80-6.00 (m, 1H, CH=), 7.18-7.48 (m, 5H, Ar-H), 8.35 (s, 1H, CH=), 8.60 (s, 1H, CH=), 8.70 and 10.68 (br s, 2H, NH_2); Anal. Calcd for $C_{14}H_{14}N_4O$: C, 66.12; H, 5.54; N, 22.03: Found: C, 66.09; H, 5.53; N, 22.06.

4-Amino-3-ethyl-5-benzylaminoethylenepyrimidin-2(3*H*)-one **(7e)**

65 %; mp 211° C; ir (KBr): 3020, 1675, 1610, 1570 cm^{-1}; ^1H nmr (DMSO-d_6) δ : 1.14 (t, J=6.5 Hz, 3H, CH_3), 3.92 (q, J=6.5 Hz, 2H, CH_2), 4.66 (s, 2H, CH_2), 7.20-7.40 (m, 5H, Ar-H), 8.12 (s, 1H, CH=), 8.36 (s, 1H, CH=), 8.45 and 10.65 (br s, 2H, NH_2); Anal. Calcd for $C_{14}H_{16}N_4O$: C, 65.57; H, 6.29; N, 21.85: Found: C, 65.15; H, 6.19; N, 22.08.

4-Amino-3-ethyl-5-phenylhydrazinoaminomethylenepyrimidin-2(3*H*)-one **(7f)**

64 %; mp 242° C; ir (KBr): 3260, 1635, 1590 cm^{-1}; ^1H nmr (DMSO-d_6) δ : 1.20 (t, J=6.5 Hz, 3H, CH_3), 4.02 (q, J=6.5 Hz, 2H, CH_2), 6.70-7.26 (m, 5H, Ar-H), 7.86 (s, 1H, CH=), 8.01 (s, 1H, CH=), 8.70 and 9.20 (br s, 2H, NH_2), 10.02 (s, 1H, CH=); Anal. Calcd for $C_{13}H_{15}N_5O$: C, 60.68; H, 5.87; N, 27.22: Found: C, 60.47; H, 5.73; N, 27.01.

4-Amino-3-ethyl-5-(4-tolylmethylene)pyrimidin-2(3*H*)-one **(7g)**

68 %; mp 262°C; ir (KBr): 1660, 1615, 1575 cm^{-1}; ^1H nmr (DMSO-d_6) δ : 1.19 (t, J=6.5 Hz, 3H, CH_3), 2.32 (s, 3H, CH_3), 4.02 (q, J=6.5 Hz, 2H, CH_2), 7.12-7.26 (m, 4H, Ar.H), 8.30 (s, 1H, CH=), 8.52 (s, 1H, CH=), 8.65 and 10.62 (br s, 2H, NH_2); Anal. Calcd for $C_{14}H_{16}N_4O$: C, 65.63; H, 6.29; N, 21.86: Found: C, 65.44; H, 6.28; N, 21.67.

4-Amino-3-ethyl-5-(4-chlorophenyl)pyrimidin-2(3*H*)-one **(7h)**

72 %; mp 265° C; ir (KBr): 2900-3300, 1665 cm^{-1}; ^1H nmr (DMSO-d_6) δ : 1.18 (t, J=6.5 Hz, 3H, CH_3), 4.00 (q, J=6.5 Hz, 2H, CH_2), 7.25-7.52 (m, 4H, Ar-H), 8.30 (s, 1H, CH=), 8.58 (s, 1H, CH=), 8.78 and 10.50 (br s, 2H, NH_2); Anal. Calcd for $C_{13}H_{13}N_4OCl$: C, 56.42; H, 4.73; N, 20.24; Cl, 12.81: Found: C, 56.21; H, 4.68; N, 20.24; Cl, 12.54.

4-Amino-3-ethyl-5-(methylpyridyl)pyrimidin-2(3*H*)-one **(7i)**

62 %; mp 236° C; ir (KBr): 2995, 2850, 1675, 1625 cm^{-1}; ^1H nmr (DMSO-d_6) δ : 1.18 (t, J=6.5 Hz, 3H, CH_3), 3.92 (q, J=6.5 Hz, 2H, CH_2), 4.68 (s, 2H, CH_2), 7.33-7.42 (m, 1H, Ar-H), 7.72 (d, J=6.5 Hz, 1H, Ar-H), 8.15 (s, 1H, CH=), 8.40 (s, 1H, CH=), 8.48 (d, J=6.5 Hz, 1H, Ar-H), 8.58 (s, 1H, Ar-H), 8.50 and 10.50 (br s, 2H, NH_2); Anal. Calcd for $C_{13}H_{15}N_5O$: C, 60.60; H, 5.87; N, 27.21: Found: C, 60,32; H, 5.77; N, 27.04.

Synthesis of 7-Amino-2-oxo-1,2-dihydropyridol [2,3-*d*] pyrimidine-6-carbonitriles (8a-b, d-e): General Procedure

To an equimolar solution of **6** *(10 mmol) and malononitrile (10 mmol) in 40 ml of ethanol,* 0.5 *ml of acetic acid* was added and the mixture was heated under reflux for 8 h. The solvent was removed in vacuo to get the residue, which was recrystallized from ethanol.

7-Amino-1-methyl-2-oxo-1,2-dihydropyrido[2,3-*d*] pyrimidine-6-carbonitrile **(8a)**

62 %; mp above 288° C (decomp.); ir (KBr): 3390, 3320, 3220, 3020, 2240, 1670, 1645 cm^{-1}; ^1H nmr (DMSO-d_6) δ : 3.52 (s, 3H, CH_3), 8.00-8.30 (br s, 2H, NH_2), 8.52 (s, 1H, CH=), 8.85 (s, 1H, CH=); Anal. Calcd for $C_8H_7N_5O$: C, 52.85; H, 3.54; N, 34.05: Found: C, 51.91; H, 3.74; N, 33.73.

7-Amino-1-ethyl-2-oxo-1,2-dihydropyrido[2,3-*d*] pyrimidine-6-carbonitrile **(8b)**

58 %; mp above 295° C (decomp.); ir (KBr): 3460, 3290, 3180, 2990, 2220, 1685, 1645 cm^{-1}; ^1H nmr (DMSO-d_6) δ : 1.22 (t, J=6.5 Hz, 3H, CH_3), 4.22 (q, J=6.5 Hz, 2H, CH_2), 8.00-8.30 (br s, 2H, NH_2), 8.52 (s, 1H, CH=), 8.85 (s, 1H, CH=); Anal. Calcd for $C_{10}H_9N_5O$: C, 55.80; H, 4.21; N, 32.54: Found: C, 55.59; H, 4.34; N, 32.43.

7-Amino-1-benzyl-2-oxo-1,2-dihydropyrido[2,3-*d*] pyrimidine-6-carbonitrile **(8d)**

55 %; mp above 310° C (decomp.); ir (KBr): 3440, 3280, 3180, 2210, 1680, 1575 cm^{-1}; ^1H nmr (DMSO-d_6) δ : 5.37 (s, 2H, CH_2), 7.20-7.45 (m, 5H, Ar-H), 8.00-8.50 (br s, 2H, NH_2), 8.55 (s, 1H, CH=), 8.90 (s, 1H, CH=); Anal. Calcd for $C_{15}H_{11}N_5O$: C, 64.97; H, 3.99; N, 25.25: Found: C, 65.22; H, 4.13; N, 25.21.

7-Amino-1-allyl-2-oxo-1,2-dihydropyrido[2,3-*d*] pyrimidine-6-carbonitrile **(8e)**

56 %; mp above 292° C (decomp.); ir (KBr): 3440, 3280, 3180, 2210, 1680, 1630 cm^{-1}; ^1H nmr (DMSO-d_6) δ : 4.80 (d, J=6.5 Hz, 2H, CH_2), 5.06-5.18 (m, 2H, CH_2=), 5.82-6.01 (m, 1H, CH=), 7.92-8.40 (br s, 2H, NH_2), 8.54 (s, 1 H, CH=), 8.88 (s, 1 H, CH=); Anal. Calcd for $C_{11}H_9N_5O$: C, 58.14; H, 3.99; N, 30.82: Found: C, 57.93; H, 4.12; N, 30.86.

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