SIMPLE AND EFFICIENT SYNTHESIS OF PYRIMIDOPYRIMIDINE AND THEIR DERIVATIVES.

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Abstract:In the present communication a simple and efficient synthesis of amino pyrimidine have been synthesized by using double michael addition reaction,in first reactionmichael acceptor ethylcyanoacetate and michael donor urea obtain 2,6-dihydroxypyrimidine which act as michael donor for further reaction with michael acceptor ethyl2,2-dicyano3,3-bis (methylthio) in the presence of catalytic amount of K_2CO_3 in DMF under reflux condition that offered 6-hydroxy-4-imino-2-(methylthio)-8-oxo-8,9-dihydro-4H-pyrimido[1,6-a]pyrimidine-3-carbonitrile and this synthesizedcompounds are used for derivatization. All synthesized compoundshave been characterized by spectralmethods.

Keywords: Michael reaction, ethyl2,2-dicyano3,3-bis(methylthio), urea.

1. INTRODUCTION:

Pyrimidines are important aromatic N-heterocycles that are found in nature, for example, as components of pyrimidine nucleotides and vitamin B1 (thiamine). Not surprisingly, the chemistry of pyrimidines has been investigated for over a century and numerous reviews have appeared[1]. Pyrimidines are also present in many drugs such as the CNS depressant phenobarbital, the anti-HIV agent zidovudine and the hyperthyroidism drug propylthiouracil. Additional pharmaceutical applications include uses as diuretics[2], anti-inflammatory[3], anti-malarial[4], and anti-tumoragents[5].

In presence of pyrimidine base thiamine, cytosine and uracil which are the essential therapeutic application. The pyrimidine represent one of the most active class of compounds possessing wide spectrum of biological activity like significant in vitro activity against unrelated DNA and RNA. The literature survey indicated that a wide range of pharmacological activities are exhibited by the compound encompassing pyrimidine nucleus. In addition to this, various analogy of pyrimidine have been found to posses antibacterial, antifungal, analgesic, antioxidant, antiviral, anticancer activities and also act as calcium channel blockers.

2.METHODS:

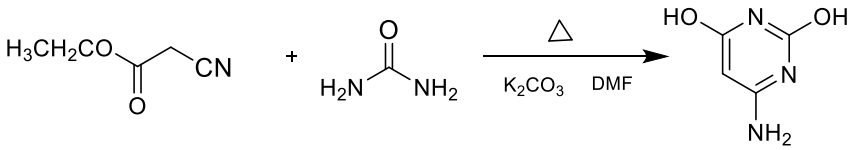
Melting point were determined in open capillary tubes and are uncorrected. The silica gel F_{254}plates were used for thin layer chromatography (TLC); the spot were examined under UV light and then developed in an iodine vapor. Column chromatography was performed with silica gel (BDH 100-200 mesh). Solvents were purified according to standard procedure. The spectra were recorded as follows; IR KBR pellets, a perkin-Elmer RX1 FT-IR spectrophotometer ; ^{1}H NMR, $CDCL_3$, 200 MHz, a varian Gemini 200 instrument. Elemental analysis was performed on a heraeus CHN-O rapid analyzer.

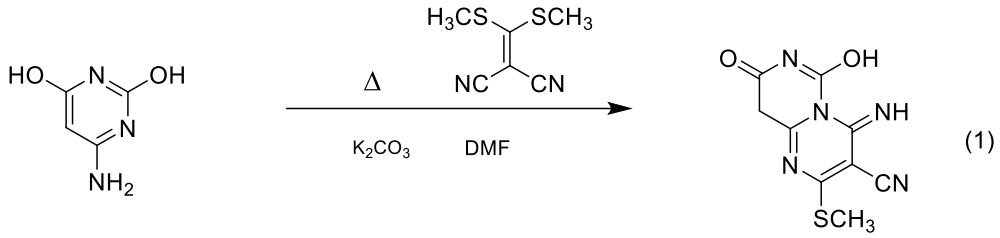
II. EXPERIMENTAL:

All solvent and reagent were obtained commercially and used as receiver, guanide nitrate($CH_6N_4O_3$), thiourea(CH_4N_2S), malononitrile ($C_3H_2N_2$), urea(CH_4N_2O), ethylcyanoacetate($C_5H_7NO_2$), DMF, K_2CO_3, Carbon disulphide(CS_2), dimethyl sulphate($C_2H_4O_4S$), KOH.

SCHEME :

Take guanidine nitrate (0.01 mole) in RBF containing DMF solvent put catalytic amount of K_2CO_3 to heat and stir. After backflow half hour, please drop ethylcyanoacetateto reflow2hour. After reaction complete then diluted with cold water and acidified. The precipitate is separated by filtration and dried under vacuum. They are crystallized by ethanol. The resulting compound 2,6 diamino4-hydroxypyrimidine, 2,6-dihydroxy pyrimidine,2,4-diamino6-mercapto pyrimidine was further reacted with ethyl 2,2-dicyano3,3-bis(methylthio) and ethyl2-cyano3,3-bis(methylthio)acrylate in the presence of catalytic amount of K_2CO_3 in DMF refluxed for 4hour that offered 6-hydroxy-4-imino-2-(methylthio)-8-oxo-8,9-dihydro-4H-pyrimido[1,6-a]pyrimidine-3-carbonitrile(1) . The compound (1) confirmed by IR, 1H and C13 NMR and MS analytical data.



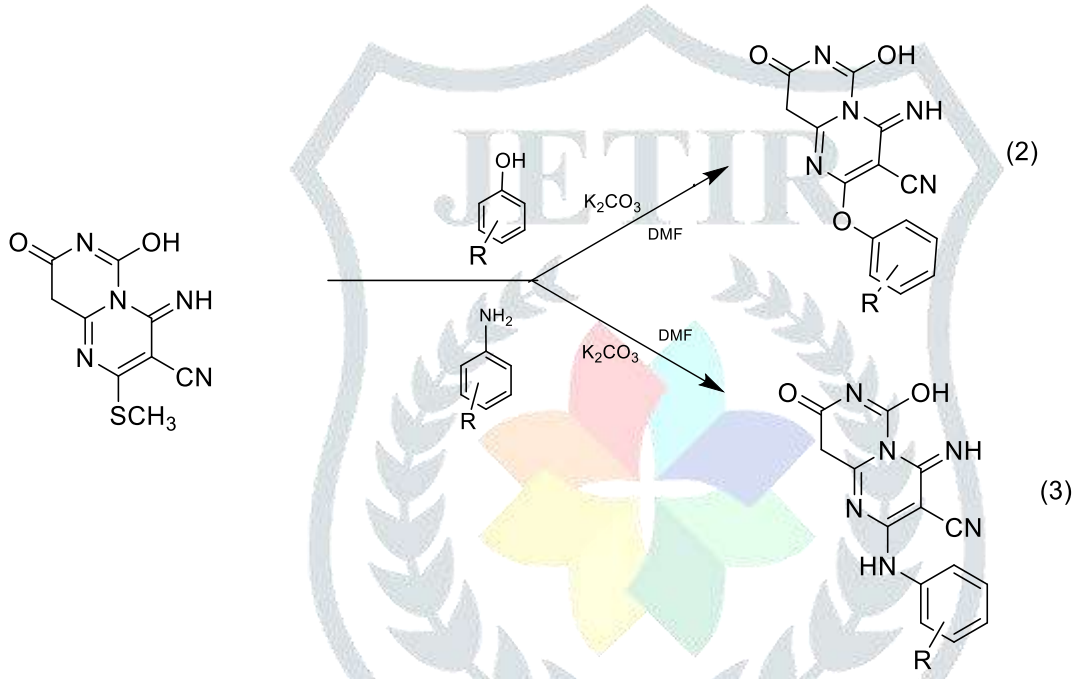


(1)

6-hydroxy-4-imino-2-(methylthio)-8-oxo-8,9-dihydro-4*H*-pyrimido[1,6-*a*]pyrimidine-3-carbonitrile

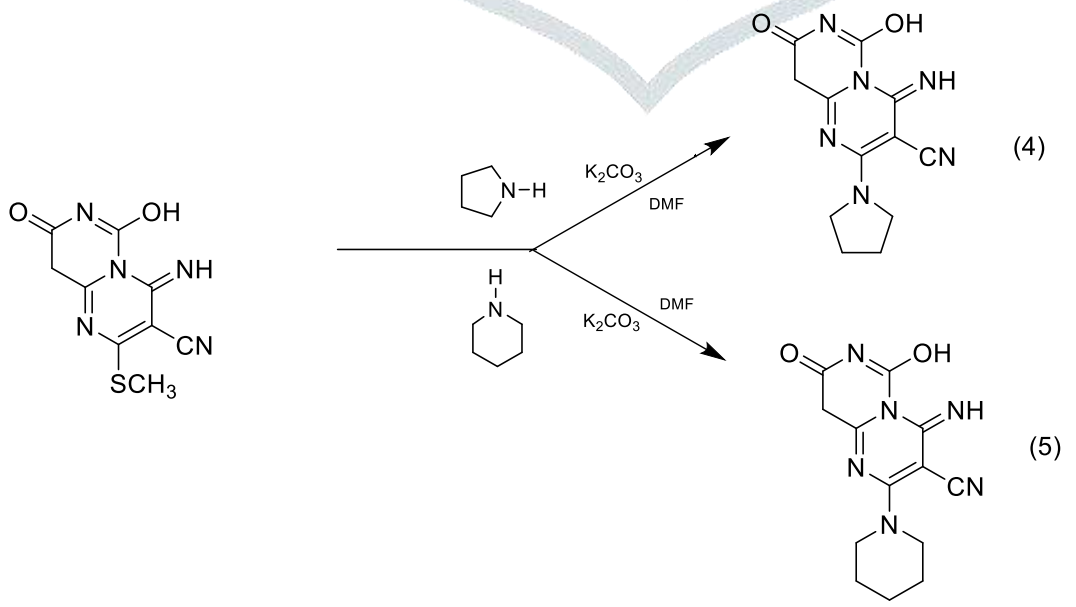
SYNTHESIS OF DERIVATIVES

A mixture of (1) and independently, various substituted aromatic amines, aromatic phenols, heteryl amines and active methylene compounds in DMF (10 ml) and anhydrous potassium carbonate (10 mg) was reflux for 4 to 6 hrs. The reaction mixture cooled to room temperature and poured into ice cold water. The separated solid product was filtered, washed with water and recrystallized using ethyl alcohol.



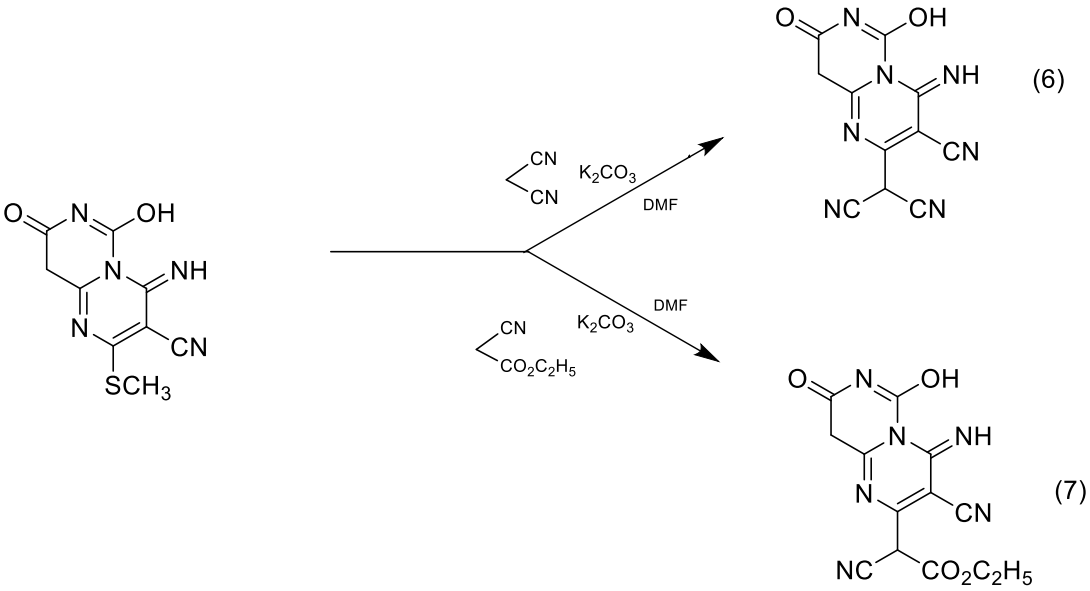
(2)

(3)



(4)

(5)



CONCLUSION:

A new different 6-hydroxy-4-imino-2-(methylthio)-8-oxo-8,9-dihydro-4H-pyrimido[1,6-a]pyrimidine-3-carbonitrile and derivatives are synthesized by using simple and efficient chemistry and this synthesized compounds act as an electrophilic species and reacting with various nucleophiles. In compounds cyano and thiomethyl groups are at adjecent position it also undergo cyclization to give polycyclic heterocyclic compound.

1) 6-hydroxy-4-imino-2-(methylthio)-8-oxo-8,9-dihydro-4H-pyrimido[1,6-a]pyrimidine-3-carbonitrile.

IR: 3340, 3430, 1580, 1640, 2250.

^{1}H NMR: δ 2.50 (S, 3H, SCH_3),δ 9.36 (S,1H, =NH), δ 2.20 (S,1H, -CH), δ 10.68 (S,1H,OH).

ESI-MS : 249.24.

Anal. Calcd for: $C_9H_7N_5SO_2$.

Mol. Formula: $C_9H_7N_5SO_2$.

Mol. Wt. 249.24.

2) 6-hydroxy-4-imino-8-oxo-2-phenoxy-8,9-dihydro-4H-pyrimido[1,6-a]pyrimidine-3-carbonitrile.

IR :3345, 3420, 1585,1650, 2230.

^{1}H NMR : δ 9.30 (s, 1H,=NH), δ 2.22 (s, 1H, -CH), δ 10.40 (s,1H,OH), δ 6.73 (d, 2H, Ar-H), δ 7.04 (dd, 2H, Ar-H), δ 6.08 (dd, 1H, Ar-H).

ESI-MS : 294.23.

Anal. Calcd for: $C_{14}H_8N_5O_2$.

Mol. Formula: $C_{14}H_8N_5O_2$.

Mol. Wt. 294.23.

3) 6-hydroxy-4-imino-8-oxo-2-(phenylamino)-8,9-dihydro-4H-pyrimido[1,6-a]pyrimidine-3-carbonitrile.

IR :3360, 3425, 1570, 1660, 2240.

^{1}H NMR : δ 9.38 (s, 1H,= NH), δ 2.3 (s, 1H, -CH), δ 11.40 (s,1H,OH), δ 6.46 (d, 2H, Ar-H), δ 7.01 (dd, 2H, Ar-H), δ 6.62 (dd, 1H, Ar-H).

ESI-MS : 293.25.

Anal. Calcd for: $C_{14}H_9N_6O_2$.

Mol. Formula: $C_{14}H_9N_6O_2$.

Mol. Wt. 293.25.

4) 6-hydroxy-4-imino-8-oxo-2-(pyrrolidin-1-yl)-8,9-dihydro-4H-pyrimido[1,6-a]pyrimidine-3-carbonitrile.

IR :3335, 3445, 1550,1640, 2260.

^{1}H NMR : δ 9.34 (s, 1H,= NH), δ 2.4 (s, 1H, -CH), δ 11.40 (s,1H,OH), δ 2.8 (t, 4H, C-H), δ 1.59 (m, 4H, C-H) .

ESI-MS : 272.26.

Anal. Calcd for: $C_{12}H_{12}N_6O_2$.

Mol. Formula: $C_{12}H_{12}N_6O_2$.

Mol. Wt. 272.26.

5) 6-hydroxy-4-imino-8-oxo-2-(piperidin-1-yl)-8,9-dihydro-4H-pyrimido[1,6-a]pyrimidine-3-carbonitrile.

IR :3345, 3455, 1540,1655, 2250.

^{1}H NMR : δ 9.34 (s, 1H,= NH), δ 2.4 (s, 1H, -CH), δ 11.40 (s,1H,OH), δ 2.7 (t, 4H, C-H), δ 1.5 (m, 6H, C-H) .

ESI-MS : 286.28.

Anal. Calcd for: $C_{13}H_{14}N_6O_2$.

Mol. Formula: $C_{13}H_{14}N_6O_2$.

Mol. Wt. 267.2.

6) 2-(3-cyano-6-hydroxy-4-imino-8-oxo-8,9-dihydro-4H-pyrimido[1,6-a]pyrimidin-2-yl)malononitrile.
IR :3365, 3450, 1575, 1645, 2240.
^{1}H NMR : δ 9.34 (s, 1H,= NH), δ 2.4 (s, 1H, -CH), δ 11.40 (s,1H,OH), δ 4.18 (s, 1H, C-H) .
ESI-MS : 391.38 .
Anal. Calcd for: $C_{11}H_5N_7O_2$.
Mol. Formula: $C_{11}H_5N_7O_2$.
Mol. Wt. 267.2.

7) ethyl2-cyano-2-(3-cyano-6-hydroxy-4-imino-8-oxo-8,9-dihydro-4H-pyrimido[1,6-a]pyrimidin-2-yl)acetate.
IR :3340, 3460, 1565,1640, 2245.
^{1}H NMR : δ 9.24 (s, 1H,= NH), δ 2.43 (s, 1H, -CH), δ 11.42 (s,1H,OH), δ 4.01 (s,1H, C-H), δ 4.12 (q, 2H, C-H), 1.30(t, 3H, C-H) .
ESI-MS : 314.25.
Anal. Calcd for: $C_{13}H_{10}N_6O_2$.
Mol. Formula: $C_{13}H_{10}N_6O_2$.
Mol. Wt. 314.25.

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