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Synthesis of 5-Cyano Uracil Derivatives and Study of their Deamination Reaction

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ABSTRACT

Facile synthesis of ureidopropenenitrileobtained by reaction of malenonitrile, orthoesterand substituted ureasat 100°C in good yields. The ureidopropenenitrile was cyclized to targeted 5-cyano Cytosine derivatives in presence of sodium ethoxide in ethanol with 60 -65% yields. The deamination of amino compound was studied to obtained uracil derivatives using ispentylnitrite.
Keywords: Ureidopropenenitrile, Substituted Urea, 5-Cyano Cytosine, One Pot Three Component Reaction.

I. INTRODUCTION

The development of efficient and mild method for synthesis pyrimidine heterocyclic compounds represents a broad area of organic chemistry [1-2]. Structures containing such as moiety often play an important role due to their biological activities these derivatives also used in cancer therapy and anti-viral research [3-6].Among these heterocyclic, pyrimidinesderivatives showed in important class of pharmaceutical discovery [7-8]. Some of these compounds are analgesics [9],antihypertensive [10], antipyretics [11] and anti-inflammatory drugs [12].Pyrimidine derivatives used in some pesticides [13], herbicides and plant growth regulators [14].Consequently synthetic methodologies for synthesis of novel pyrimidine or fused pyrimidine compounds are of particular interests in the medicine and agro chemistry[15].

The development of alternate and efficient strategies is of considerable interest in literature and various methods were reported towards pyrimidine synthesis [16-19].
The development of new chemotherapeutic agents is becoming the major interest in many academic and industrial research laboratories all over the world with the aim to discover newer molecules, with higher specificity and reduced toxicity than existing ones. In addition, various types of new resistant microorganisms that are being discovered now days are the great challenge for scientists. Uracils occupy a distinct and unique place in medicine.
The cytocines and uracils derivativesare very important compounds. Various workers had been carried out the synthesis of these compounds.
We have reported the synthesis of these compounds by conventional method. The product obtained by this method was identical, confirmed by scanning the IR, NMR, MP, mixedMP and TLC method.

II. EXPERIMENTAL WORK

2.1 Materials and methods

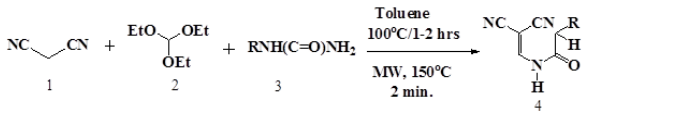
Melting points were determined on a Gallenkamp melting point apparatus. The 1H (300 MHz) and 13C (75MHz) NMR spectra were recorded on a Varian XL-300 Spectrometer. Chemical shifts were reported in ppm relative to tetramethylsilane (TMS), and multiplicities are given as s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). Infrared spectra were recorded as KBr pellets on a Shimadzu FTIR-408 spectrophotometer. Mass spectra were recorded on a Shimadzu LC-MS:EI QP 2010A mass spectrometer with an ionization potential of 70eV. Elemental analyses were performed on Quest flash 1112 Series EA Analyzer. Reactions were monitored by thin layer chromatography (TLC), carried out on 0.2 mm silica gel 60 F254 Merck plates using UV light (254 and 366 nm) for detection and for column chromatography 5-20µm (Merck, 60-120 mesh) silica gel is used. Column dimension is 39× 2 cm and elution volume is 200-400 mL. Common reagent-grade chemicals are either commercially

available and were used without further purification or were prepared by standard literature procedures.

III. RESULTS AND DISCUSSION

The synthesis of cytosine derivatives was carried out in two steps. All the new compounds were well characterized by IR, NMR and elemental analysis given in experimental section.

3.1 Synthesis of ureidopropenenitrile, 4a-c



3a,R=Ph ;3b,R=CH_2 Ph;3c,R=CH_3

Theureidopropenenitrile**4**was prepared by using malononitrile**1,** triethylorthoformate**2**and substituted urea **3.** The reaction mixture was stirred in toluene at 100^o Cfor 1 hr. The completion of the reaction was checked by TLC, run in mixture ofHexane:Ethyl acetate (8:2). The solid precipitated on cooling was filtered and washed with ether to get required intermediate product **4**in60-65 % yield.

To prepared the same product in microwave, the above reaction mixture in round bottom flask attached with condenser was irradiated for 2 min. After cooling the flask, the obtained solid was stirred in 5 ml ether and then filtered to furnish **4** in 80-85 %

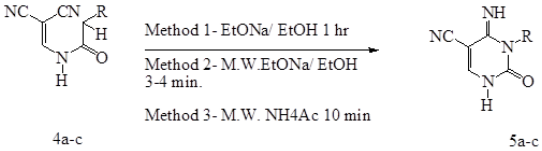
Table 3.1. The following table showing the detail for the synthesis of 3-cyano ureidopropenenitrile**4a, c**

1	Parameters	4a	4b	4c
2	Reaction Time in hrs.	1	1	1
3	Amount of solvent (ml)	20	25	20
4	% Yield	60	68	65
5	M.P. ^oC	265	258	245

The structure of the ureidopropenenitrile4,was also confirmed by analytical and spectroscopic studies.

e.g. The I.R. of **4c** showed the peaks at 3300 cm^{-1}, 2202 and 1667 was due to –NH_2, CN, and amide carbonyl respectively.The ^{1}HNMR($CDCl_3$) showed singlet at δ 2.73 for three protons of methyl group. The broad singlet at δ 7.15 and 10.73 corresponds to two NH protons and the sharp singlet at δ 8.38 is for =CH. The elemental analysis of compound **4a** is also in agreement with the molecular formula $C_6H_6N_4O$. Based on the above spectral and analytical data we have assigned the structure **4a**1-(2, 2-dicyanovinyl)-3-phenylurea for this product. The spectral and physical data for all compounds are explain in experimental part

3.2 Synthesis of 5-Cyano Cytosine derivatives, 5(a-c)



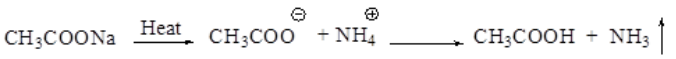
4a,R=Ph ;4b,R=CH_2 Ph;4c,R=CH_3

Method 1:

The ureidopropenenitrile**4a-c**, obtained in above method was cyclized to the required cytosine i.e. 5-cyano -4-aminopyrimidone. Compound **4** was refluxed in sodium ethoxideinethanol for 1 -2 hrs. Completion of the reaction was confirmed by TLC. The solvent was removed under vacuum. The residue was dissolved in cold water; then solid product was neutralization with 2N HCl, was filtered, and washed with water and purified. Yield obtained were **60-65%.**

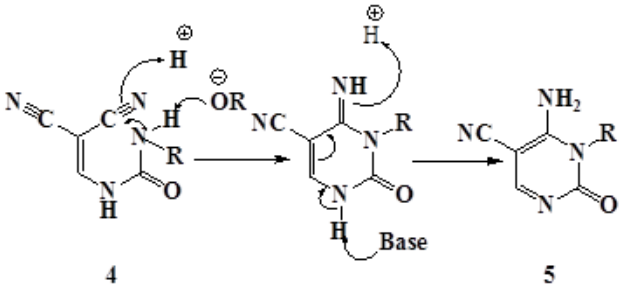
Method 2:

The same reaction also carried out in microwave using CH_3ONa/ CH_3OH(strongbase) for 3 minutes and furnished 60-67 % yield. ORThe above reaction mixture was heates in at 100^{o}Cfor NH_4OAC. The molten NH_4OAC acts as solventfor the reaction and also create weak basic medium due to evolution of $NH_3$by its decomposition. The use of NH_4OAC is novel eco friendly methods use for cyclization of ureidopropenenitrile



The ammonium acetate is non-toxic,non-poisonous, eco –friendly reagent. The products **5a-c** wascharacterized by analytical and spectral data.

Mechanism for cyclization reaction:



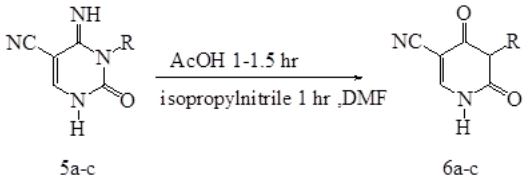
4 5

e.g.The I.R. spectrum **5a** showed the presence of NH_2 frequency at 3288 $cm^{-1}$and 3400 $cm^{-1}$and 2219 cm^{-1} corresponds to CN,the amide C=O observed at 1667 cm^{-1}.The ^{1}HNMR($CDCl_3$) showed multipletat δ 7.20-7.60 for aromatic protons. The sharp singlet for =C-H (olefin protons) is obtained at δ 8.40. Broad singlets at δ 7.15 and 10.73 correspond to two NH_2 protons. The elemental analysis this compound correspond molecular formula $C_{11}H_8N_4O$.

Table 3.2. The following table shows detail for the synthesis of compounds **5a,**

Parameters	5a	5b	5c
Reaction Time in hrs	1	1	1
Amount of solvent ml	20	2	20
% Yield	50	55	45
M.P. °C	282	270	251

3.3 Synthesis of Uracil Derivatives, 6a-cDeamination:



5a-c 6a-c

6a,R=Ph ;6b,R=CH_2 Ph;6a,R=CH_3

The removal of NH_2 group from the compound is deamination. The deamination of 4-amino -5-cyanopyrimidine 5a-c yield valuable product 5-cyano uracil **6a-c** by refluxing on glacial acetic acid.

Method 1:

The removal of NH_2 group from the compound is deamination. The deamination of 4- amino-5- cyano pyrimidine 5a-c yield valuable product 5-cyano uracil **6a-c**on using isopentylnitrile in DMF.

The identity of the products by both methods was proved by MP, TLC, IR and ^{1}HNMR methods.

e.g.The I.R. spectrum **6a** showed the presence of two carbonyls frequency at1746 $cm^{-1}$and the peak at 1668 $cm^{-1}$and CN at 2226 cm^{-1}.But no peakwas observed for NH_2 in the IR indicates the primary aminegroup of compound 5awhich was observed at 3388 cm^{-1} has been converted to carbonyl group.Similarly, the ^{1}HNMR showed 5 aromatic protonsappeared as amultiplet at δ 7.27-7.50. Broad singlet at δ 10.73correspond to NHprotons.The sharp singlet for =C-H (olefin protons) isobtained at δ 8.58.Theelemental analysis this compound correspond molecular formula $C_{11}H_7N_3O_2$.

Table 3.3. The following table shows detail for the synthesis of compounds **6a, c**

Parameters	5a	5b	5c
Reaction Time (hrs)	1	1.5	1
Solvent (ml)	20	25	20
% Yield	58	52	46
M.P.°C	264	247	233

IV. CONCLUSION

We have explored a facile and efficient protocol for the synthesis of 5-Cyano Cytosine derivatives with 60-89% yields. Particularly valuable features of present method include broad substrate scope, short reaction time, straight forward procedure and easy aqueous work up that facilitated 80-85% recovery of pure product and use of inexpensive chemicals and reagents.

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VI. REFERENCES

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