Introduction

Pyrimidine derivatives have gained unique importance in the field of medicinal chemistry. Pyrimidine also known as m-diazine is the parent substance of a large group of heterocyclic compounds. Compounds belonging to this group were known as breakdown products of uric acid from very early date in the history of organic chemistry. Pinner\(^1\) studied the ring system systematically and used the name pyrimidine for the parent nucleus.

Pyrimidines can be referred as a cyclic amidine and the chemical behavior of these derivatives is dominated by this fact. In terms of the reactivity positions 2,4 and 6 are similar whereas position 5 stands somewhat different being more aromatic in character.

Pyrimidine forms an integral part of a large number of therapeutically important compounds like thiamine, riboflavin, purinbases, sulfadiazine etc. The role of pyrimidine derivatives in biochemical process is now known with reasonable accuracy and the researchers in this field are regularly adding to our knowledge, the chemistry and biochemistry of pyrimidine derivatives. Quite a good number of pyrimidine derivatives have been found to have physiological activities like antihepatitis B virus\(^2-5\), anticonvulsant\(^6,7\), anti-Rubella\(^8,9\), antimicrobial\(^10-16\), anti-inflammatory\(^17-28\), antitumor\(^20-36\), antibacterial\(^37,38\), antiviral\(^39-48\), calcium channel modulators\(^49\), anti-HIV-1\(^50-51\), anti-herpesvirus\(^52,53\), antimitotic\(^54\), antineoplastic\(^55\), antifungal\(^56\), antifolate\(^57\), leishmanicides\(^58\), serotonin and dopamine receptors\(^59\), aromatase inhibitors\(^60\), glycinamide ribonucleotide transformylase with potent cell growth inhibition\(^61\) and selective pneumocystis carinii dihydrofolate reductase inhibitors\(^62\) etc.
Methods of preparation

A number of methods have been reported in literature for the synthesis of pyrimidine derivatives. They can be mainly classified into three types according to fundamental nature of the fragments which combine together to form pyrimidine nucleus. The three basic types of synthesis can be schematically represented as follows (Fig. I).

**Type I**

This is a common type adopted for synthesizing pyrimidine derivatives. In this the cyclization is usually involves a double condensation with the elimination of water, alcohol or hydrogen halide between amino and carbonyl, carboxylic acid, carboxylic ester and chloride or enol ether groups or condensation by addition of amino to cyano groups or to polarized double bonds without an elimination reaction.

**Type II**

In this the aminomethylene compound is formed as an intermediate by the action of ethoxymethylene compound with ammonia or iminoether, amide or amidine with reactive methylene compound. This amino methylene compound then undergoes cyclization with the reagents like imino ether, amide, amidines, etc. producing pyrimidine derivatives.

**Type III**

This type of pyrimidine synthesis involves the insertion of a single
carbon atom between the nitrogens of 1,3-diamine to produce hydrogenated pyrimidine.

Grimaux\(^63\) condensed urea with malonic acid in the presence of phosphoryl chloride and obtained barbituric acid (Fig. II).

\[
\text{H}_2\text{N} - \text{NH}_2 + \text{HO} - \text{CO} - \text{CO} - \text{OH} \xrightarrow{\text{POCl}_3} \text{HO} - \text{N} - \text{N} - \text{OH}
\]

Fig. II

Later, this method was modified by Michael\(^64\) by condensing malonic ester with urea using sodium alkoxide as a catalyst. This process finds application in the preparation of barbiturate drugs\(^65\).

Behrend\(^66\) originally showed that \(\beta\)-keto esters\(^67\) or their enol ethers\(^68\) are suitable reagents for condensation with urea in the preparation of 4-methyl uracil.

\(\beta\)-Diketones also undergo condensation with urea under similar experimental conditions as those used in \(\beta\)-keto esters\(^69\) to give pyridines.

Biginelli\(^70\) synthesized dihydropyrimidines by the condensation of urea, \(\beta\)-Keto ester and aldehyde while Karn Folkers et al.\(^71\) have synthesized various 2-keto-6-methyl-5-carboxoxy-4-substituted phenyl-1,2,3,4-tetrahydropyrimidines by applying Biginelli reaction. The reaction sequence as shown in (Fig. III).

\[
\text{H}_2\text{N} - \text{NH}_2 + \text{R} - \text{CHO} + \text{Me} - \text{COOEt} \xrightarrow{\text{}} \text{O} - \text{N} - \text{H} - \text{R}
\]

Fig. III
Folker\textsuperscript{72} have synthesised 2-keto-4-benzyl-5-phenyl-1,2,3,4 tetrahydro-pyrimidine with 65\% yield by condensing phenyl acetaldehyde and acetophenones with urea in absolute ethyl alcohol containing conc. hydrochloric acid.

Condensation of benzoyl acetone, an aldehyde and urea\textsuperscript{73} accelerated by hydrochloric acid, proceeded smoothly by Biginelli reaction affording 2-oxo-1,2,3-4-tetrahydropyrimidines having 5-acetyl or 5-benzoyl groups as shown in (Fig. IV).

![Fig. IV]

A number of 4-substituted 5-acetyl-2-oxo-6-methyl-1,2,3-4-tetrahydro pyrimidines\textsuperscript{74} were prepared by acid catalysed condensation of urea with acetyl acetone and various aldehyde.

Whitehead\textsuperscript{75} described a new and quite general synthesis applicable to a wide variety of pyrimidines. Ethyl orthoformate reacts with urea or thiourea which on heating gives N,N'-dicarbamyl formamidine. Reaction of N,N'-dicarbamyl formamidines with active methylene compounds in boiling ethylene dichloride gives ureido ethylenes. The ureido ethylene undergo ready cyclization with diethyl malonate in the presence of a basic catalyst to give corresponding pyrimidines. The reaction sequence may be depicted as under (Fig.V).
Thiourea undergoes all the cyclization reactions of urea but with considerably greater ease, since 2-thiol group may be readily converted into other substituents like -H, -OH and -SR etc. S-alkyl thioureas are more reactive & condenses readily with β-Keto ester\textsuperscript{76} and their enol ethers\textsuperscript{77} yielding 2-alkylthiopyrimidines (Fig. IX).

Similarly, thiourea also reacts with malonic esters\textsuperscript{78}, β-keto esters\textsuperscript{79} or their enol ethers\textsuperscript{80}, cyanoacetic esters\textsuperscript{81}, malononitrile\textsuperscript{82} and α-β-unsaturated carbonyl compounds\textsuperscript{83}.

Zimmerman et al.\textsuperscript{84} condensed various β-hydroxy and α-β-unsaturated
ketones with thiourea in the presence of alkoxide and obtained the corresponding 4,6-disubstituted 2-thiono-4-hydroxy hexahydropyrimidines.

From the above reactions, it is clear that all these cyclization involve the nucleophilic attack of nitrogen atom on the electrophilic center of a carbonyl group. Therefore, basicity of nitrogen is an important factor in determining the ace of reaction. Thus thiourea is more reactive than urea and their O- and S- alkylated tautomers are still more reactive.

Guanidine, the strong base finds very convenient application in the synthesis of pyrimidine derivatives. Condensation with guanidine is generally carried out in alcoholic media in presence of alkali. Strong acid has also been used as a catalyst in some reactions. Synthesis of pyrimidines from guanidine and β-ketoester, β-diketones, enol ethers, cyanoacetic esters, α-β-unsaturated carbonyl compounds have been reported in literature. Reaction of guanidine with β-ketoester to give pyrimidine is written as follows (Fig.VII).

Substituted guanidines eg. alkyl and aryl guanidines, dicyandiamide, arylsulfonyl guanidines and arylbiguanidines are reported to react with β-ketoester, β-diketones, enol ethers, cyanoacetic esters, α-β-unsaturated carbonyl compounds etc. to yield 2-substituted amino pyrimidine derivatives (Fig. VIII).
Pinner found that amidines condenses with acetoacetic ester, yielding 2-substituted-6-hydroxy-4-methyl pyrimidines. Similarly, amidines undergoes condensation reaction with $\beta$-keto ester, $\beta$-dicarboxylic acid, and $\beta$-diketones.

4-amino-5-cyano-2-methyl pyrimidines are prepared by condensation of acetamidine with ethoxymethylene malonitrile and ethoxymethylene malonic ester respectively.

Milcent had described the synthesis of alkyl 2-amino-4,6-diaryl-1,4-dihydropyrimidine-5-carboxylates from alkyl 3-aryl-2-benzoylpropenoates and guanidine in presence of an inorganic base.
unreacted unsaturated ketone to give 2,4,6-trisubstituted pyrimidines (Fig. X).

![Image of chemical structure](image)

**Fig. X**

**Selection of Method**

Impressed by the concerted endeavors that have been made by a large number of workers to synthesize various pyrimidine derivatives of physiological and pharmacological importance, it was thought worthwhile to synthesize reported and some new pyrimidine derivatives. With this moderate objective in mind, a number of pyrimidine derivatives have been synthesized by adopting the Biginelli’s method.

The selection of this method was made on the basis of following facts:

1. Starting materials are easily available.
2. Yields are quantitative.
3. Simple experimental techniques are required.

Various dihydropyrimidinones and their thione analogues are synthesized by using various catalyst like Sulphamic Acid (H$_2$NSO$_3$H), Zirconyl Oxy chloride ZrOCl$_2$.8H$_2$O and Chlorosulfonic acid (ClSO$_3$H) discussed in section-A, section-B and section-C of this chapter.
Section A

Sulphamic acid catalyzed synthesis of 3,4-dihydropyrimidin-2(1H)-ones and their thione analogues

Describing more than one century ago by Biginelli dihydropyrimidinones (DHPMS) have now been recognized as vital drugs in the antihypertensive treatment as well as calcium channel blockers, α-1a-antagonists and neuropeptide Y (NPY) antagonists. Some of them are batzeladine alkaloids which have been found to be potent HIV gp 120-CD4 inhibitors. DHPMS and their sulphur analogues are pharmacologically important because of their antibacterial, antitumour and anti-inflammatory properties. The biological activity of some recently isolated alkaloids has also been attributed to the presence of dihydropyrimidinone moiety in the corresponding molecule.

In 1893 Biginelli reported the first synthesis of DHPMS by a simple one-pot condensation reaction of ethyl acetoacetate, benzaldehyde and urea. In the follow decades the original cyclocondensation reaction had been extended widely to include variation in all three components, allowing access to a large number of multifunctionalized DHPMS derivatives. However, it suffers from low yields of the product particularly in the case of substituted aromatic and aliphatic aldehydes. Recently several methods have been reported for preparing dihydropyrimidines using different Lewis acid such as BF₃·OEt₂, LaCl₃, La(OTf)₃, Yb(OTf)₃, ZnCl₂, ZnBr₂, ZrCl₄, BiCl₃, Bi(OTf)₃, LiBr, LiClO₄,Mn(OAc)₃, CAN, FeCl₃·6H₂O, NiCl₂·6H₂O etc. as well as protic acids such as H₂SO₄, HOAc, Conc. HCl as promoters. Many other methods including microwave irradiation, ionic liquids and clay are also reported. However, most of these methods are associated with expensive and toxic reagents, stoichiometric amount of catalyst, long reaction time, unsatisfactory yields, incompatibility with other functional groups and involve difficult product isolation procedures. Moreover, some of those
methods are only practical for aromatic aldehydes\textsuperscript{109,110}. Thus there is still a need for a simple and general procedure for one-pot synthesis of dihydropyrimidinone and their thione analogues under mild conditions.

Sulphamic acid (H$_2$NSO$_3$H, SA), which is a common organic acid with mild acidity, involatility and incorrositvity, is insoluble in common organic solvents. It is a very stable white crystalline solid\textsuperscript{112} and has already been demonstrated that SA is composed not of the amino sulfonic acid but of $^\text{+H}_3\text{NSO}_3^-$ zwitterionic units by both X-ray and neutron diffraction techniques.\textsuperscript{113,114} During the last few years, SA has emerged as a promising solid acid catalyst for acid catalyzed reaction, \textit{viz.} acetalization,\textsuperscript{115} esterification,\textsuperscript{116-118} acetylation of alcohols and phenols,\textsuperscript{119} nitrile formation.\textsuperscript{120} Very recently, SA has been used as a chemoselective catalyst for the transesterification of $\beta$-ketoesters\textsuperscript{121} and Beckmann rearrangement.\textsuperscript{122} The unique catalytic feature and intrinsic zwitterionic property of SA is very different from the conventional acidic catalyst, which prompted us to explore the further application of SA as an acidic catalyst in other carbon-carbon and carbon-heteroatom bond forming reaction.

Present Work

In the present work we have reported a simple and efficient method for the synthesis of 3,4-dihydropyrimidines using SA as a catalyst. The three component mixture of an aldehyde, 1,3-dicarbonyl compound and urea or thiourea was refluxed in ethanol in presence of catalytic amount of SA for 40-70 minute to give corresponding dihydropyrimidines in 85-95\% yield. Most importantly, aromatic aldehydes carrying either electron donating or electron withdrawing substituents reacted very well to give the desired product in excellent yield (Table IIA). Even
aliphatic aldehyde, which normally show poor yields in the Biginelli reaction, afforded the products with high yields (Table IIA).

**General procedure**

To synthesize the title compounds following starting materials have been used.

1. Aldehyde
   a. Benzaldehyde
   b. 4- Nitro Benzaldehyde
   c. 4- Chloro Benzaldehyde
   d. 4- Hydroxy Benzaldehyde
   e. 3-Nitro Benzaldehyde
   f. Pyridine-4-Carbaldehyde
   g. 2-Chloro Benzaldehyde
   h. Furan-2-carbaldehyde
   i. 4-Trifluoromethyl-Benzaldehyde
   j. Formal
   k. Methanal
   l. n- Pentanal

2. 1,3 dicarbonyl compound
   a. Ethyl acetoacetate
   b. Methyl acetoacetate

3. Urea

4. Thiourea
3,4-Dihydropyrimidin-2(1H)-ones and their thione (4a-4w)

A mixture of 1,3 dicarbonyl compound (10 mmol), aldehyde (10 mmol) urea or thiourea (15 mmol) and SA (2 mmol) in ethanol was heated at 50°C for appropriate time as mention in table I. The reaction was monitored by TLC. After completion of reaction, the reaction mixture was poured into ice water and the precipitated solid was collected by filtration, washed with water and dried. The crude product thus obtained was recrystallised from ethanol to give pure compound as white solid.

Structure of the newly synthesized compounds was established by the spectral analysis.
Experimental Protocol

Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyridimidine-5-carboxylate (4a)

A mixture of ethyl acetoacetate (10 mmol), benzaldehyde (10 mmol) urea (15 mmol) and SA (2 mmol) in ethanol was heated at 50°C for 45 minute. After completion of reaction, the reaction mixture was poured into ice water and the precipitated solid was collected by filtration, washed with water and dried. The crude product thus obtained was recrystallised from ethanol to get 4a. M. P. 201-203°C, Yield- 94%.

All other compounds of this series were synthesized by following above procedure. The characterization data of these compounds have been recorded in Table IIA.

Discussion of Spectra:

Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyridimidine-5-carboxylate (4a)

IR spectra of some of the representative compounds of this series have been scanned on JASCO spectrophotometer using KBr pellets. Chemical shifts are reported in cm⁻¹.

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<th>Wavenumber (cm⁻¹)</th>
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<td>3245</td>
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<tr>
<td>2980</td>
<td>C-H stretching (aromatic)</td>
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<tr>
<td>1702</td>
<td>O=C-OEt stretching</td>
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<tr>
<td>1648</td>
<td>O=C-NH stretching</td>
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¹H NMR spectra were recorded on Varian Gemini 200 MHz spectrometer. Chemical shifts are reported in δ units (ppm) relative to TMS as internal standard using DMSO-d₆ as a solvent.
Electron spray ionization mass spectra (ES-MS) were recorded on Water-Micromass Quattro II spectrometer.

Mass (ES/MS): m/z 259 (M - H) +
A Search For Pharmacologically Active Nitrogen Heterocycles: Pyrimidine
A Search For Pharmacologically Active Nitrogen Heterocycles : Pyrimidine
Table IIA: Characterizations data of 3,4-dihydropyrimidin-2(1H)-ones and their thione analogues (4a-4w):

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<th>Time (min.)</th>
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