RESEARCH ARTICLE

SYNTHESIS OF PYRIMIDONE AND THIOPYRIMIDONE DERIVATIVE

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ABSTRACT:

In this study some important methods of synthesis of pyrimidine and thiopyrimidone have reviewed. The Six member heterocycles are an important class of heterocyclic compounds like thiopyrimidone which contains four carbon atoms and two nitrogen in their ring structure. The pyrimidone base i.e. Thymine, Cytosine, and Uracil are important building block of nucleic acid DNA and RNA such enormous naturally occurring structural entities make them valuable molecule in heterocyclic synthesis.

KEYWORDS: *Pyrimidine, Thiopyrimidine, Urea, Thiourea, Chalcones.*

INTRODUCTION:

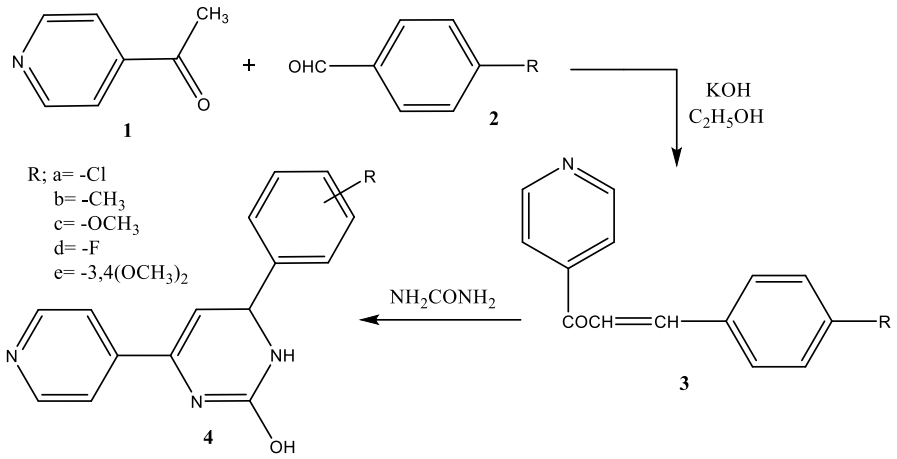
The pyrimidone or pyrimidine is one of the simple members of pyrimidone family. It is heterocyclic compounds which consist of four carbon atom and two nitrogen atoms in their cyclic ring structure. The pyrimidine was isolated between 1837 and 1864. Some important and well known biologically valuable compounds are Cytosine, Thymine, and Uracil. The Cytosine is very important nitrogenous base derived from pyrimidine which is present in nucleic acid. The pyrimidone molecule has Antitubercular activity [1-3], Antibacterial activity [4-5] some of its derivatives act as Antianginal drug [6] particularly used in the treatment of heart disease usually occurs due to not sufficient blood flow to heart. The compound containing pyrimidone functionality shows Antihypertensive effect [7] and Antiplatelate and Antithrombic activity[8] particularly used for preventing myocardial infraction and to reduce formation of blood clot [9].

The dihydropyrimidone was synthesized by Chemist Biginelli by using condensation reaction of 1, 3 dicarbonyl compound, benzaldehyde and urea this result in to pyrimidone derivative similarly pyrimidonethione have been synthesized by this method but thiourea is used in place of urea. The Six member heterocycles are an important class of heterocyclic compounds like thiopyrimidone which contains thio carbonyl group , four carbon atom and two nitrogen in their ring structure.

The compounds built-in thiopyrimidone nucleus served as Anti-histamine [10], antimalarial [11] Analgesic Antipyretic drug [12]. The important classes of pyrimidine derivatives are pyrimidine-thione

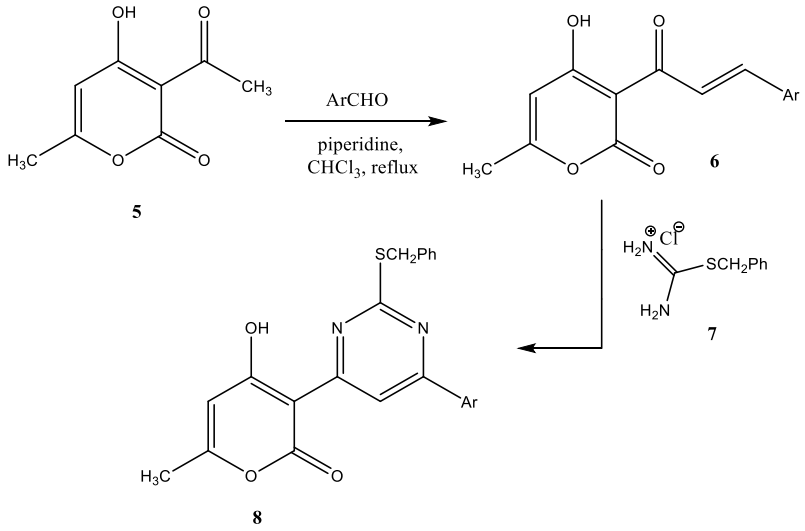
and its derivatives in these compounds the ring thiocarbonyl sulpher atom is serve as an interesting replacement for existing ring carbonyl oxygen atom of pyrimidone thus thiopyrimidone derivatives used in the preparation of Inhibitor of hepatitis C virus [13] and used for treatment of hepatitis. The thiopyrimidone have cytotoxic effect [14] and also act as chemotherapeutic agent and have remarkable antitumor activities used as anti-cancer [15-16]. Some synthetic methods of pyrimidine and thiopyrimidone are reviewed here in schemes.

Monica Kachroo, Rakesh Panda *et al* [17] have been extensively studied and developed Method of synthesis of pyrimidine **4** by reaction of Pyridinyl ketone **1** subdtituted benzaldehyde 2 in presence of pattasium hydroxide converted in to an intermediate chalcone 3 which on further treatment with urea afforded to di phenyl substituted pyrimidine **4** shown in (**Scheme-1)**.



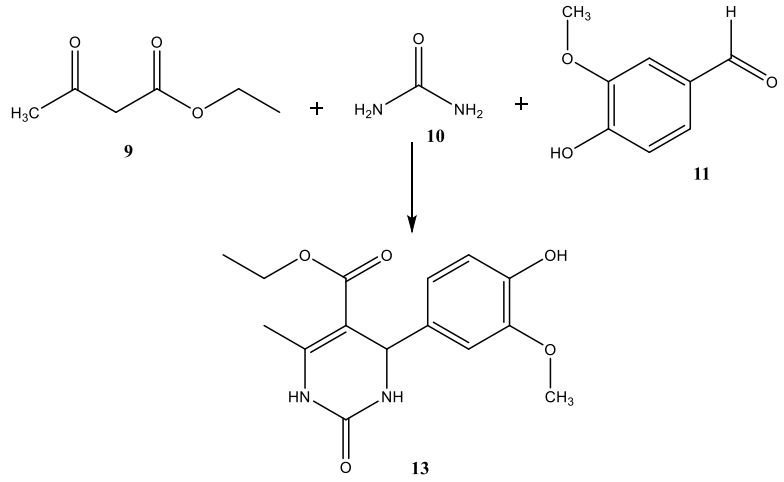
SCHEME 1

Navgeet Kaur, Ajay K Agarwal *et al* [18] extensively studied devised synthesis of benzylthio-pyrimidin-4-yl-4- pyran-2-one 8 by reaction of precursor 3-acetyl-4-hydroxy-6-methyl-2H-pyran-2-one 5 with benzaldehyde in presence of piperidine as base resulted in to chalcone derivative 6 which on further reacted with 2-benzylisothiouronium chloride 7 resulting in to formation of compound 8 shown in (Scheme-2)



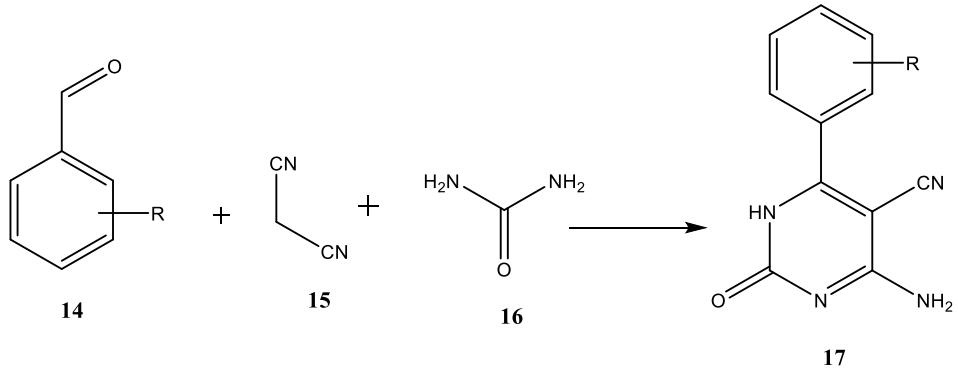
SCHEME 2

Kappe C O and Co-worker [19] carried out multi component synthesis of pyrinmidone derivative by reaction of ethyl acetoactate **9,** Urea **10** and 4-hydroxy-3-methoxy beanzaldehyde **11** converted in to pyrimidine derivative **12** shown in **(Scheme-3)**



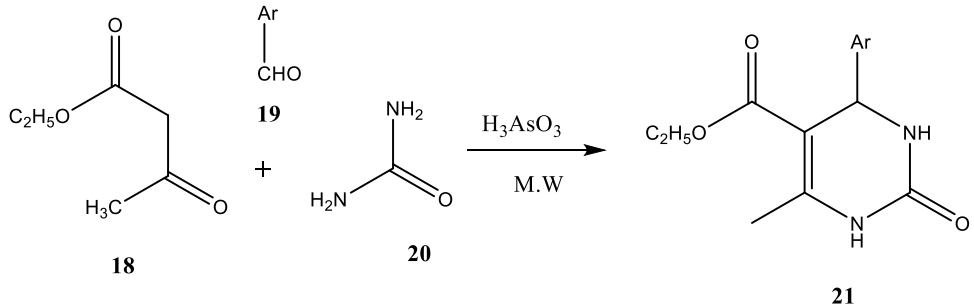
SCHEME 3

Dhongade SR, Divate V A, *et al*[20] attempted synthesis of phenyl substituted pyrimidine derivatve by three component reaction of substituted benzaldehyde with **14**, Mthylene dinitrile **15** and Urea **16** furnished in to compound **17** shown in **(Scheme-4)**



SCHEME 4

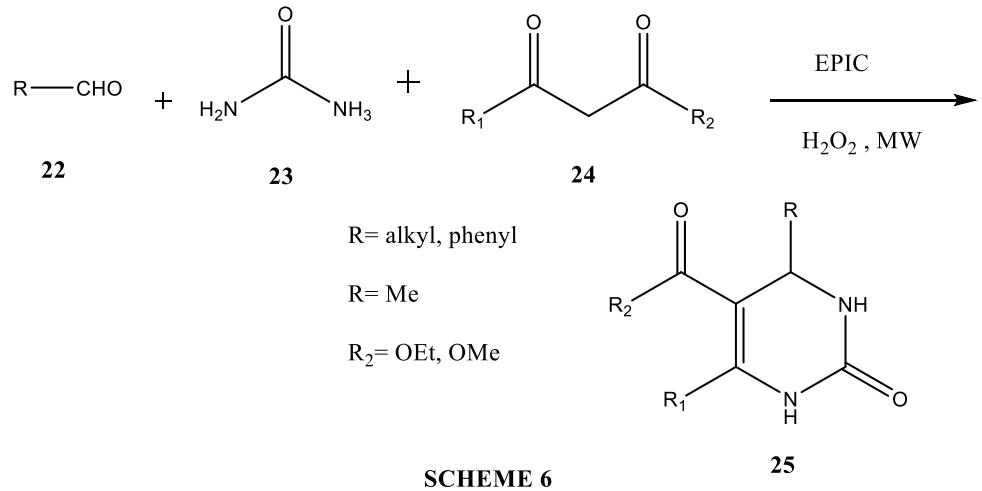
P A Patil, R P Bhole, *et al*[21] have developed new method of synthesis of pyrimidine derivative **21** by reaction of acetoacetic ester **18** benzaldehyde **19** and urea **20** in presence of arsenic acid upon microwave irradiation formation of compound **21** shown in **(Scheme-5)**



SCHEME 5

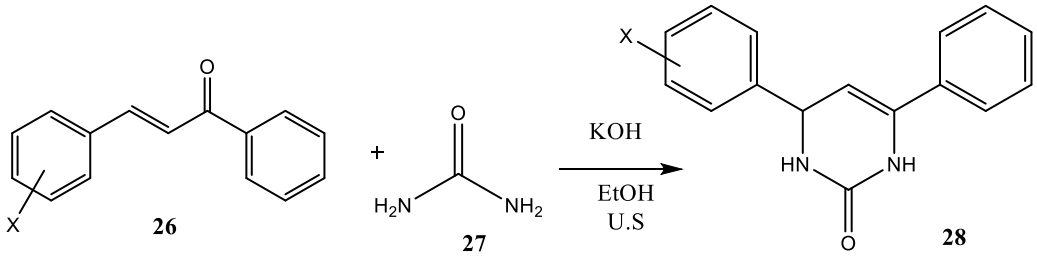
Makone Sangita Sanjay *et al* [22] have developed new synthetic protocol of synthesis of substituted pyrimidine derivative by multicomponant reaction of aldehyde **22** Urea **23** and dicarbonyl

compound 24 inpresnce of EPIC catalyst and irradiated with microwave afforded to compound **25** shown in (**Scheme-6)**



SCHEME 6

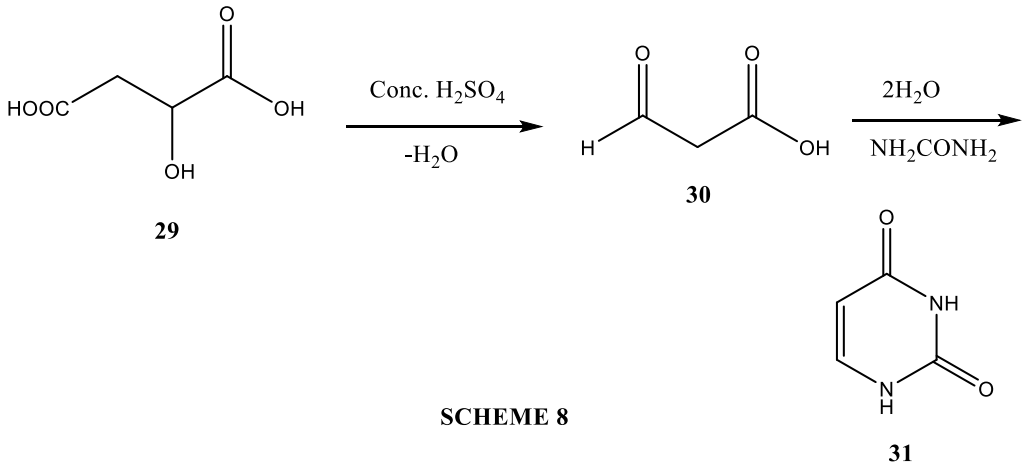
Javad Safaei-Ghomi, Mohammad Ali Ghasemzadeh *et al* [23] the ultra sound synthetic method has been developed for synthesis of phenyl substituted pyrimidine derivative. In protocol chalcone **26** and urea **27** have sonicated under ultrasound irradiation in presence of base KOH result in the formation of compound **28** shown in (**Scheme-7)**



X=a=H, b=2-CH_3, c= 3-CH_3, d=4-CH_3, e=2-OCH_3, f=4-OCH_3, g=2,4-OCH_3,h=N(Me)2

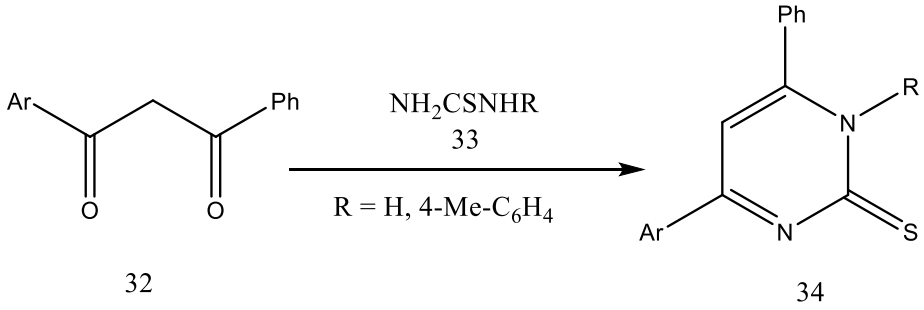
SCHEME 7

Method due to Rao N V, N Vaisalini *et al*[24] have develop synthesis of pyrimidine starting from precursor 3-hydroxy butandoic acid **29** which have been converted in to compound **30** which have further condensed with urea afforded to pyrimidone **31** shown in (**Scheme-8)**



SCHEME 8

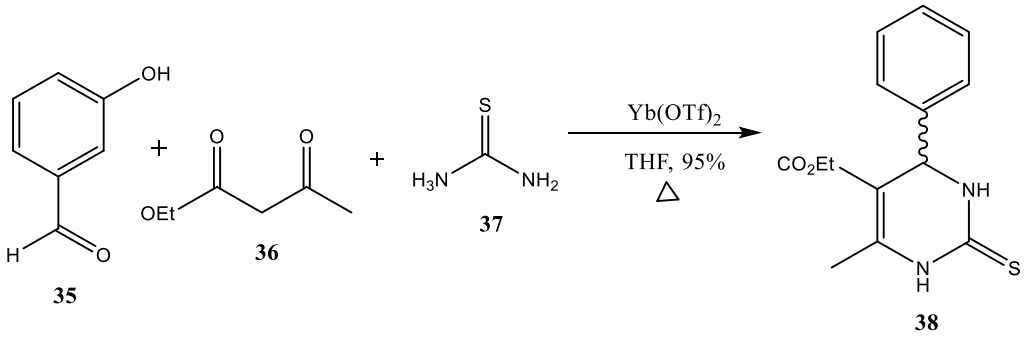
Method due to Utala P S, Raghuwanshi P S *et al* [25] have devised synthesis of N-substituted pyrimidone thione by reaction of dicarbonyl compound **32** with N-substituted thio urea **33** resulted in the formation of compound **34** shown in (**Scheme-9)**



32 34

SCHEME 9

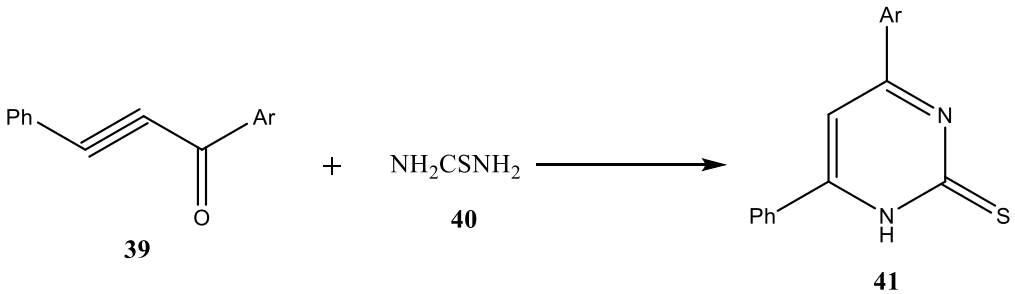
Method due to Dondoni A, Massi A, *et al* [26] designed synthsis of thiopyrimidone derivatives by three component reaction of Meta hydroxyl benzaldehyde **35** ethyl acetoacetate **36** and thiourea **37** in presence of Ytterbium(II) Triflate as a catalyst in THF as solvent resulted in the formation thiopyrimidone derivatives **38** shown in (**Scheme-10)**



35 **36** **37** **38**

SCHEME 10

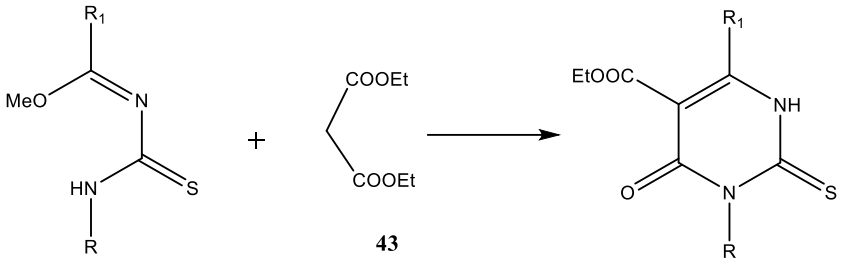
Cupta V S, Huennekens F M. *et al* [27] have develop simple method of synthesis of pyrimidinethione by reaction of alkyne ketone **39** with Thiourea **40** afforded to compound **41** shown in (**Scheme-11)**



39 **40** **41**

SCHEME 11

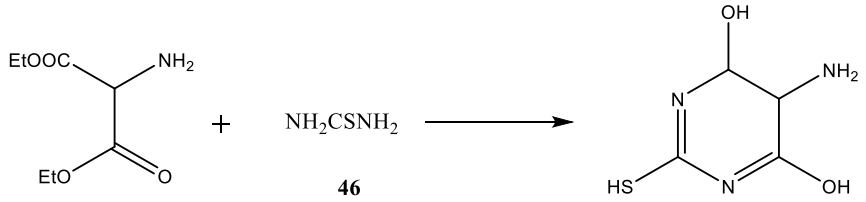
Krech J., Miguel Z A, *et al* [28] have developed new method of synthesis of pyrimidone thione derivative in this protocol substituted thio urea **42** on treatment with diester **43** coonverted in to compound **44** shown in (**Scheme-12)**



42 **43** **44**

SCHEME 12

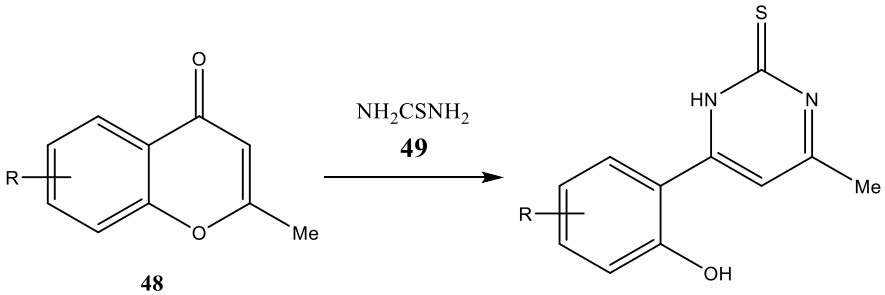
Coenen H H, Olsson R A *et al* [29] have devised synthesis by reaction of diethyl 2-aminomalonate **45** with thiourea **46** upon condensation furnished in to compound **47** shown in **(Scheme-13)**



45 **46** **47**

SCHEME 13

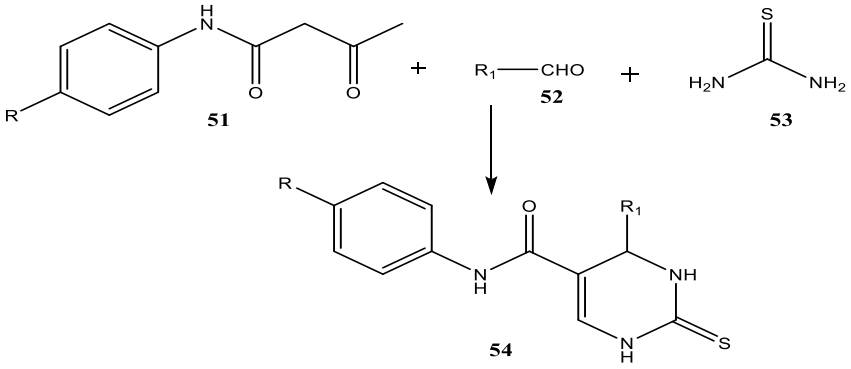
Method due to Ibrahim S S *et al* [30] have developed method of synthesis from 2-methyl-4H-chromen-4-one **48** which on further treatment with thiourea **49** converted in to compound **50** shown in **(Scheme-14)**



48 **49** **50**

SCHEME 14

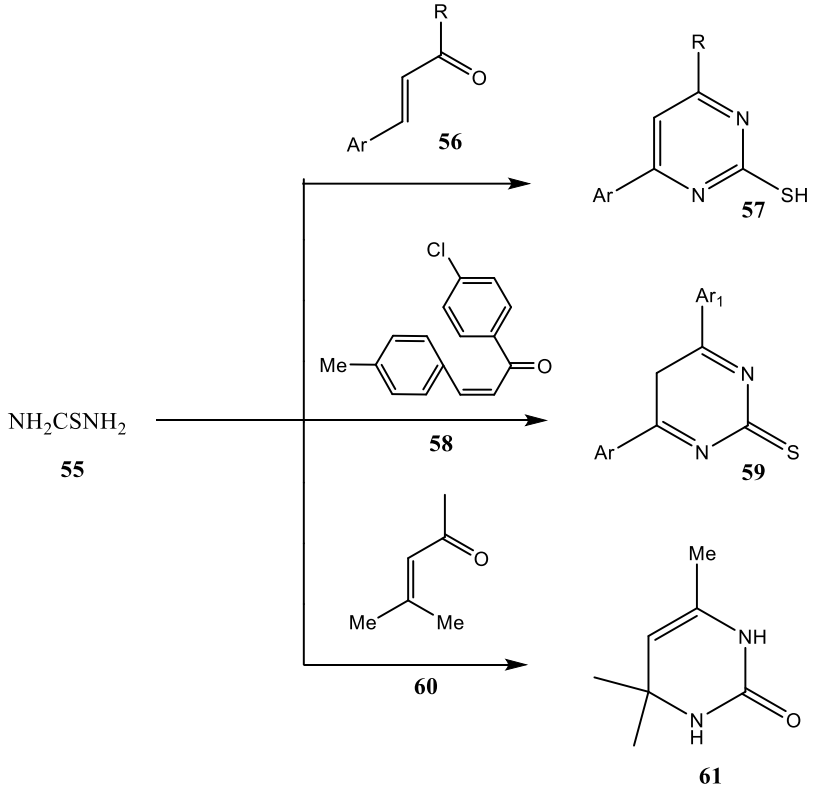
K Venkatesan *et al* [31] have developed new method of synthesis of pyrimidine thione derivative by condensation of three component 3-oxo-N-phenylbutanamide **51** aldehyde **52** and thiourea **53** converted in to compound **54** shown in **(Scheme-15)**



51 **52** **53** **54**

SCHEME 15

Khalaf Z H, Yanni A S *et al* [32] have developed synthesis of various thioperimidone derivatives from thiourea is an important precursor. Thiourea on treatment with chalcone **56**, **58** and **60** converted in to pyrimidine thione derivative **57**, **59** and **60** respectively shown in **(Scheme-16)**



SCHEME 16

CONCLUSION:

This review throws light from starting of isolation of pyrimidone in 1873 to synthesis of pyrimidine derivative by Chemist Biginelli and then by various researchers has developed synthetic protocols. Which includes conventional non-conventional synthesis, microwave assisted synthesis and ultrasound assisted synthesis of pyrimidone and thiopyrimidone derivatives. Starting compounds like chalcone and dicarbonyl compounds simply undergoes ring closure reaction with reagents like urea and thiourea lead to formation of heterocyclic which resemble building block of biomolecule like DNA and RNA. The research on pyrimidone and thiopyrimidone has grater greater importance in pharmacy and modern drug development.

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