Solvent-free synthesis of pyrimido[4, *5-d*]pyrimidine derivatives using Ammonium metavanadate as a catalyst at room temperature

Report of a project carried out as a part of curriculum for the Degree of Master of Science in Organic Chemistry

CHO-453

Submitted by

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Affiliated to

Savitribai Phule Pune University, Pune

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DECLARATION BY THE CANDIDATE

I hereby declare that this project entitled "**Solvent-free synthesis of pyrimido[4, *5-d*]pyrimidine derivatives using Ammonium metavanadate as a catalyst at room temperature"**is a confide and genuine project work carried out by us under supervision of **Dr. Amol Haridas Kategaonkar**, Assistant Professor, P.G. Department of Organic Chemistry, M.V.P. Samaj's K.S.K.W. Arts, Commerce and Science College CIDCO, Dist. Nashik Maharashtra.

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CERTIFICATE BY THE SUPERVISOR

This is to certify that entitled "**Solvent-free synthesis of pyrimido[4, *5-d*]pyrimidine derivatives using Ammonium metavanadate as a catalyst at room temperature**" is a bonafide and genuine project work done by **MR. KHAIRNAR HARSHAD ANNA** partial fulfilment of the requirement for degree of Master of Science (Organic Chemistry)

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EXAMINERS' CERTIFICATE

This is to certify that PG dissertation entitled "**Synthesis Of Pyrimido[*4, 5-D*]Pyrimidine Derivatives Using Ammonium Metavanadate (H_4NO_3V) As A Catalyst At Room Temperature.**" submitted by **MR. HARSHAD ANNA KHAIRNAR** was carried out by the candidate under supervision of **DR. AMOL H. KATEGAONKAR.**

With this understanding, we consider the fact that the PG dissertation is a well written project report, should be appreciable and the project work carried out is commendable, we recommend that the PG dissertation submitted by **MR. HARSHAD ANNA KHAIRNAR** be accepted in its present form for the award of Master of Science in Organic Chemistry, Savitribai Phule Pune University, Pune. He is successfully defended the Viva-Voce Examination.

15.07.2024

(EXTERNAL EXAMINER) (INTERNAL EXAMINER)

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Our acknowledgement is many more what we have expressed here.

Date: -

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MR. KHAIRNAR HARSHAD ANNA

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INDEX

1. Introduction

Combinatorial chemistry is playing an increasingly important role as one of the tool of modern medicinal chemistry for the rapid discovery of new leads.[1] The preparation of libraries of small organic molecules is a rapidly evolving area of research.[2] Pyrimido pyrimidines are annelated uracils that have attracted considerable interest in recent years. Derivatives of pyrimido pyrimidine are known to display a wide range of pharmacological activities, and their potent inhibitory properties regarding the tyrosine kinase domain of epidermal growth factor receptor,[3] 5-phosphoribosyl-1-pyrophosphate synthetase[4] and dihydrofolate reductase[5] have been fully demonstrated. Numerous reports delineate the antitumour,[6] antiviral,[7] antioxidant,[8] antifungal and heptatoprotective activities.

Multi-component reactions (MCRs)[9] are masterpieces of synthetic efficiency and reaction design. Therefore, mastering unusual combinations and sequences of elementary organic reactions under similar conditions is the major conceptual challenge in engineering novel types of MCR. Most advantageously and practically, MCR can often be extended into combinatorial[10] and solid phase syntheses promising manifold opportunities for developing novel lead structures of active agents, catalysts and even novel molecule based materials. Inevitably, many classical heterocyclic syntheses are MCR that are based upon carbonyl group condensations. Hence, medicinal chemistry is largely found on these easily accessible heterocyclic frameworks. The use of multicomponent reactions (MCRs) to generate interesting and novel, drug-like scaffolds is replete in the recent chemical literature.[11] For novel Biginelli-like scaffold synthesis, the use of the common open chain β-dicarbonyl compounds in Biginelli reactions has been extended to the use of cyclic β-diketones,[12] β-ketolactones,[13] cyclic β-diesters or β-diamides, benzocyclic ketones and α-keto acids. All of these reactions were performed using conventional heating and reaction times were long.

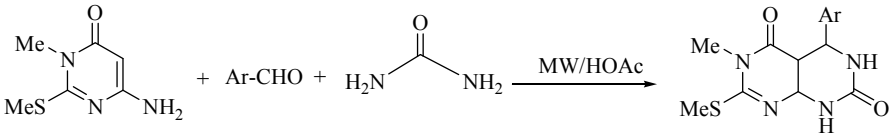
Solvent-free reactions are well known as environmentally benign methods that also usually provide improved selectivity, enhanced reaction rates, cleaner products and manipulative simplicity.[14] However, these procedures are practically limited as the solvents in microwave oven at elevated temperatures create high pressures, which may cause explosion. To circumvent these problems, there is a need for the development of newer methods which proceed under mild and solvent free condition. Solvents are often used to pre-absorb the substrates on to, and wash the products off the solid support. Benefits from using solvent-free approaches include improved

safety by avoiding low-boiling solvents that would otherwise cause undesirable pressure increases during heating. For the transition of microwaves to the reactants, the solid support is the best option. Moreover they also provide an opportunity to work with open vessels and an enhanced possibility of upscalling the reactions on a preparative scale.[15]

Nowadays solvent-free synthesized reactions much importance because of the absence of solvents coupled with the high yields and short reaction times often associated with reactions of this type make these procedures very attractive for organic synthesis. Earlier reported procedures for the synthesis of pyrimido[4, *5-d*]pyrimidines typically involved longer reaction time and less yield.[16] In the present section, we would like to describe the advantages of dry reaction techniques coupled with stirring at room temperature and their applications to organic synthesis using solid supports.[17]

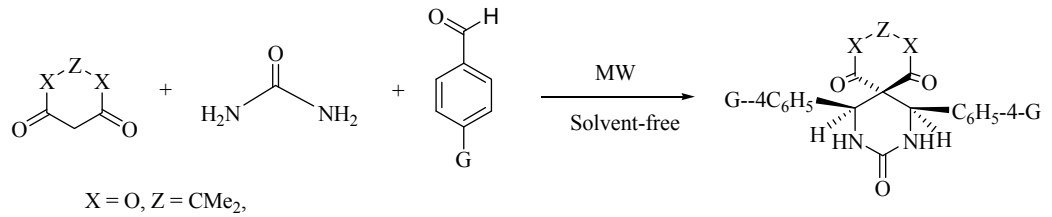
2. Literature Review

Dabiri *et al.*[18] synthesized primido [4,5-*d*] pyrimidines by reacting 6-amino-3-methyl-2(methylthio) pyrimidin-4(3*H*)-one, aldehyde and urea under microwave assisted condition (Scheme 1)



Scheme 1

Shaabani and Bazgir[19] reported Spiro-fused heterocycles were synthesized in good to high yields by a pseudo four-component reaction of an aldehyde, urea and a cyclic β-diester or a β-diamide such as Meldrum's acid or barbituric acid derivatives using microwave irradiation under solvent-free conditions (Scheme 2).

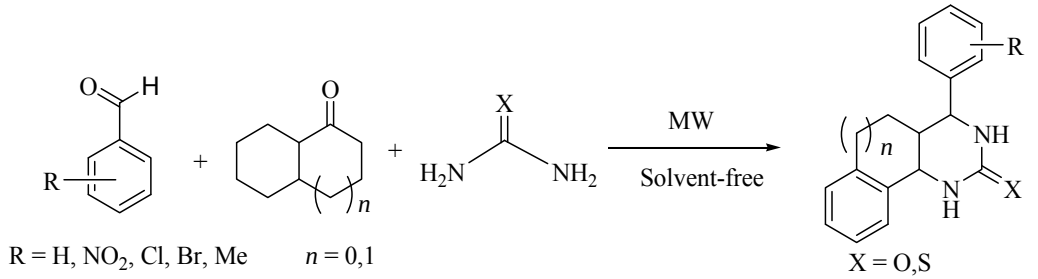


X = O, Z = CMe_2,

X = NH_2/NMe_2, Z = CO

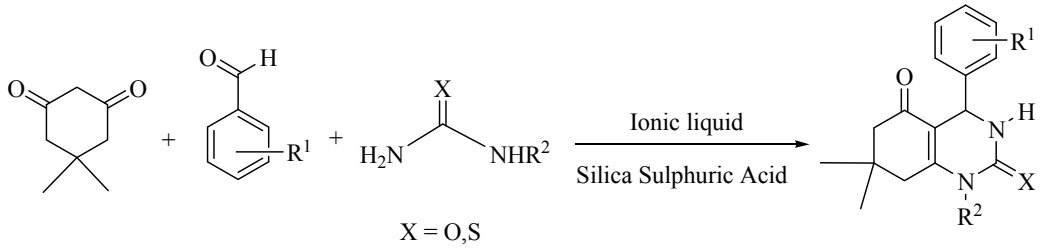
Scheme 2

Mirza-Aghayan *et al.*[20] described A novel and efficient one-pot method for the preparation of fused ring 3,4-dihydropyrimidin-2(1*H*)-ones and thiones from cyclocondensation of aldehydes, cyclic ketones and urea or thiourea using a catalytic amount of cupric chloride under mild conditions reaction (Scheme 3).



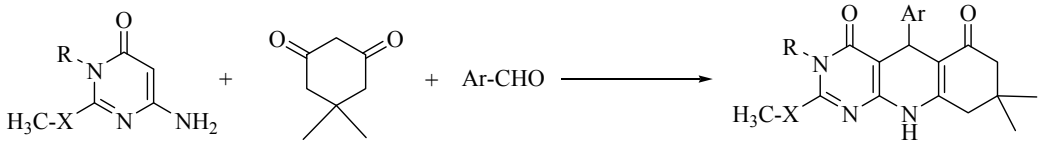
Scheme 3

Shaabani *et al.*[21] reported, Biginelli-like scaffolds were synthesized in good yields by a three-component condensation reaction of 5,5-dimethyl-1,3-cyclohexanedione, an aldehyde and urea, *N*-methylurea or thiourea in 1-butyl-3-methylimidazolium bromide ([bmim]Br) as ionic liquid (IL) in the presence of silica sulfuric acid (SSA) as solid acid catalyst at 100 °C within less than 2 hours (Scheme 4).



Scheme 4

Quiroga *et al.*[22] described pyridopyrimidine–spirocyclohexanetriones and pyrimido[4,5-b]quinolinones were obtained in a three-component microwave-assisted reaction of 6-aminopyrimidin-4-ones with dimedone and formaldehyde solution or paraformaldehyde, respectively (Scheme 5).

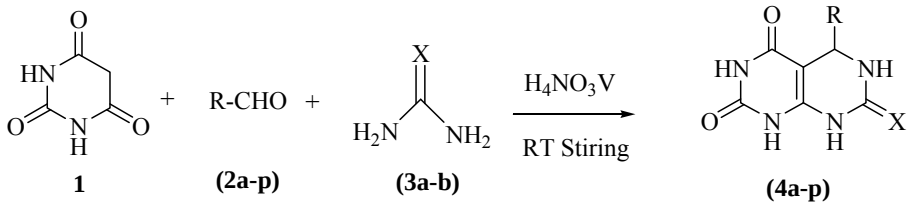


Scheme 5

3. Present Work

Pyrimido[4, 5-d]pyrimidine derivatives were synthesized by using an efficient, facile and solvent-free procedure using ammonium metavanadate (H_4NO_3V). Ammonium metavanadate (H_4NO_3V) is soluble in water. The resulting solutions contain moderate concentrations of hydrogen ions and have P^{H}'s of less than 7.0. They react as acids to neutralize bases. These neutralizations generate heat, but less or far less than is generated by neutralization of inorganic acids, inorganic oxoacids and carboxylic acid therefore we go for this catalyst due to its best catalytic efficiency to promote some organic reactions.[23]

The reaction time has been brought down from long minutes to short minutes with improved yield as compared to reported method (Scheme 6).



1 **(2a-p)** **(3a-b)** **(4a-p)**

Scheme 6

4. Results and Discussion

We describe a expeditious solventless stiring approach for the rapid assembly of pyrimido[4, 5-d]pyrimidines. Aromatic aldehydes (**2a-p**, 0.01 mmol) on reaction with barbituric acid (**1**, 0.01 mmol) and urea/ thiourea (**3a-b**, 0.01 mmol) using dry conditions with ammonium metavanadate(10%) catalyst yielded corresponding pyrimido[4, 5-d]pyrimidines (Scheme 6).

The synthesis of pyrimido[4, 5-d]pyrimidines requires acidic condition to promote the reaction we have considered ammonium metavanadate promote the reaction. Several aromatic aldehydes having electron donating and withdrawing groups underwent the conversion to form a series of pyrimido[4, 5-d]pyrimidines . The physical characteristics of ammonium metavanadate are slightly acidic. The reaction conditions are mild and the work-up procedure is simple. The products were isolated

in high yields (90–98%). The structures of the products were determined from their spectral data.

The role of ammonium metavanadate has been proposed to activate the aldehyde by binding the oxygen atom of aldehyde with vacant 'd' orbital of transition metal vanadium, to achieve the stable oxidation state, and hence the reaction rate increases tremendously to shorten the reaction time within 1-3 minutes at room temperature. A further study revealed that even 10 mol% of the catalyst was sufficient to forward the reaction within the minimum time period. Using optimized reaction parameters, a number of pyrimido[4, 5-d]pyrimidines **(4a-4p)** (Scheme 6) were synthesized. Also To the best of our knowledge, there are no earlier reports on the preparation of pyrimido[4, 5-d]pyrimidines using Ammonium metavanadate as a catalyst.

In summary, a novel approach for the synthesis of pyrimido[4, 5-d]pyrimidines has been explored by using ammonium metavanadate as a catalyst, which showed several advantages: mild reaction conditions (at room temperature), shorter time period, operational and experimental simplicity.

Table 1 Synthesis of pyrimido[4, 5-d]pyrimidine derivatives using ammonium metavanadate (H_4NO_3V)

Compound	R	X	Time Reported (min)	Yield(%)[a]	M. P.(°C)
4a	C_6H_5	O	2.3	95	247-250
4b	2-OH C_6H_4	O	3.0	96	218-220
4c	4-Cl C_6H_4l	O	1.2	96	294-295
4d	4-OMe C_6H_4	O	2.0	97	285-287
4e	4-CH_3 C_6H_4	O	1.3	96	248-250[b]
4f	4- OH C_6H_4	O	2.4	91	210-212[b]
4g	4-$N(CH_3)_2$ C_6H_4	O	3.0	90	255-257[b]
4h	4-OH, 3-OMe C_6H_4	O	2.3	94	275-277[b]
4i	4-NO_2 C_6H_4	O	2.1	91	202-204[b]
4j	4-Br C_6H_4	O	1.4	92	210-212[b]
4k	2-Cl-3-Quinolinyl	O	3.0	95	282-284
4l	Piperonyl	O	2.0	94	294(d)
4m	C_6H_5	S	2.3	95	294-295
4n	2-OH C_6H_4	S	3.0	94	198-200
4o	4-Cl C_6H_4l	S	3.0	98	280(d)
4p	4-OMe C_6H_4	S	2.3	96	>300(d)

[a]Isolated Yields. [b]Newly synthesized compounds

5. Conclusion

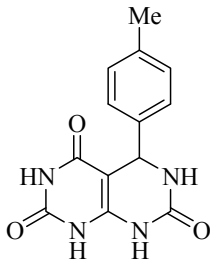
We have described an improved, efficient and one pot synthesis of pyrimido[4, 5-d]pyrimidine derivatives via a three-component cycloaddition reaction. Another advantage of this method is excellent yields in shorter reaction time with high purity of the products.

6. Experimental Section

General procedure for the synthesis of compounds (24a-p)

A mixture of barbituric acid (0.01 mmol), an aromatic aldehyde (0.01 mmol), urea or thiourea (0.01 mmol) and ammonium metavanadate (H_4NO_3V) stirred at room temparature for appropriate time (Table 1). Progress of reaction was monitored by thin layer chromatography using ethyl acetate: hexane (2:8) solvent system. After completion of reaction, the reaction mixture was cooled to room temperature and poured on crushed ice. Recrystallization was done in dimethyl formamide.

7. Spectral Analysis

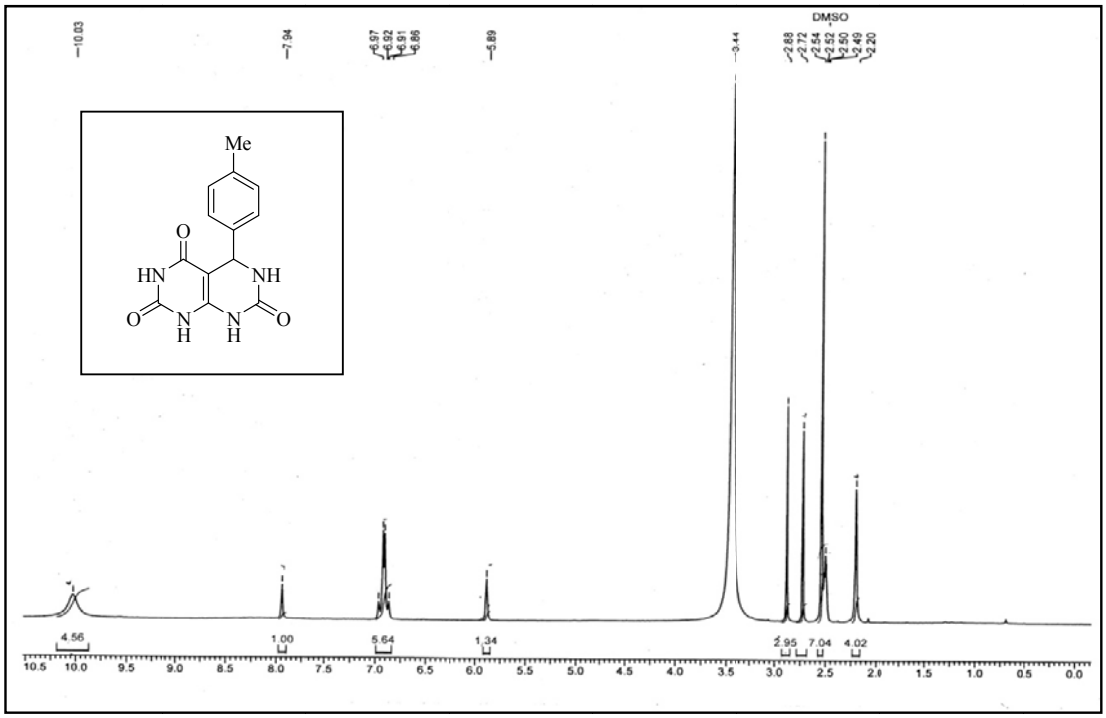


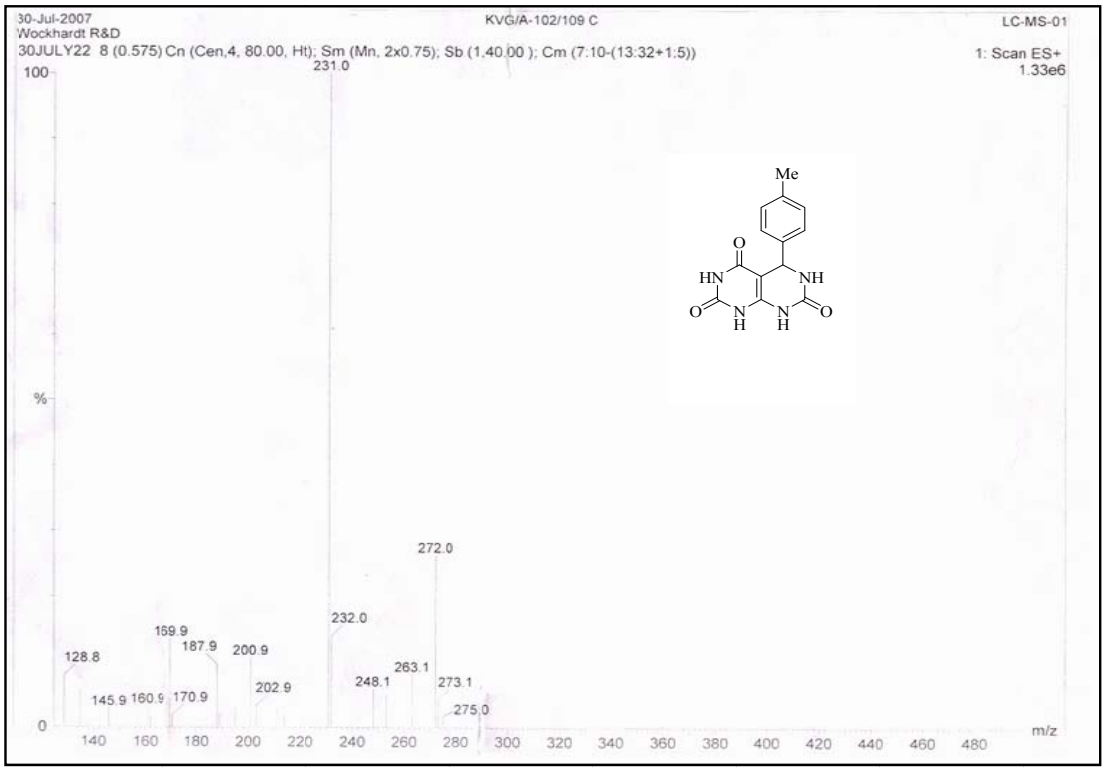
5,6-dihydro-5-p-tolylpyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,8H)-trione **(4e)**

IR (KBr, cm^{-1}): 3490, 3250, 3125, 2867, 1697, 1616, 1468.

^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 10.93(s, 2H, NH), 10.03(s, 1H, NH), 7.94(s, 1H, NH), 6.97-6.86(m, 4H, H_{arom}), 5.89(s, 1H, 5-H), 2.88(s, 3H, CH_3).

ES MS: m/z 273.1 (M+1).


DMSO
Me
HN
NH
O
N
H
4.56
1.00
5.64
1.34
2.95
7.04
4.02


30-Jul-2007
Wockhardt R&D
KVG/A-102/109 C
LC-MS-01
30JULY22 8 (0.575) Cn (Cen,4, 80.00, Ht); Sm (Mn, 2x0.75); Sb (1,40.00); Cm (7:10-(13:32+1:5))
1: Scan ES+
1.33e6
231.0
272.0
232.0
159.9
187.9
200.9
128.8
263.1
248.1
273.1
202.9
145.9
160.9
170.9
275.0
Me
m/z

4.3.8 References

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