

Recent Developments in the Synthetic Chemistry of Pyrimido [4, 5-d] pyrimidine Derivatives : A Systematic Review

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ABSTRACT

This review focuses on the recent development of synthesis of pyrimido [4, 5-d] pyrimidine derivatives. Pyrimido [4, 5-d] pyrimidine derivatives are important heterocyclic compound which possess diverse pharmacological activities such as anticancer, antitumor, antioxidant, antiviral, antibacterial anti-allergic and anti-inflammatory activities. Therefore, organic chemists are interested in the synthesis of these bioactive heterocycles. In this review, we have compile the recent literature report of various synthetic procedures for synthesis of pyrimido [4, 5-d] pyrimidine derivatives.

Keywords: Pyrimido [4, 5-d] pyrimidine, Heterocyclic compound, Pharmacological activities, Synthesis.

I. INTRODUCTION

Nitrogen containing heterocyclic compound have enormous significance in the field of chemistry. Pyrimidines are important molecules that possess unique biological activities and pharmaceutical properties due to their similarity to natural pyrimidine bases (uracil, cytosine, thymine, adenine, and guanine) which make them highly effective in certain biological processes. Pyrimido pyrimidine such as pyrimido [4, 5-d] pyrimidine possesses efficient pharmacological activities including

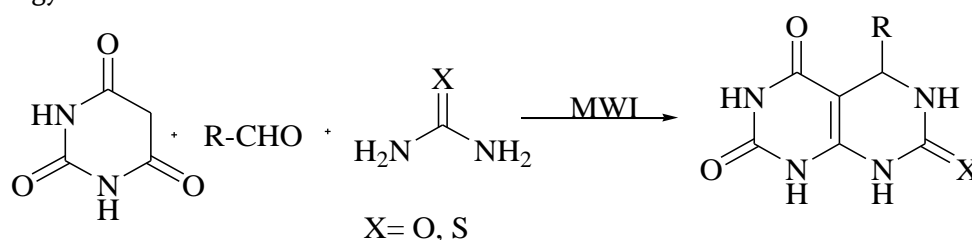
anticancer [1], antitumor [2], antioxidant [3], antiviral [4], antibacterial [5], anti-allergic [6], anti-inflammatory [7], antihypertensive [8] and hepatoprotective [9]. In addition, they also possess effective inhibitory properties such as tyrosine kinase receptor [10], 5-phosphoribosyl-1-pyrophosphate synthetase [11] and dihydrofolate reductase [12]. Therefore, organic chemists are interested in the synthesis of these bioactive heterocyclic compounds. In recent year several methods that have been described for the synthesis of pyrimido [4, 5-d] pyrimidine derivative due to their significance in

bioorganic and medicinal chemistry. The present review article focuses on various synthetic methods for the synthesis of pyrimido [4, 5-d] pyrimidine derivative reported in recent scientific literature.

II. SYNTHETIC METHODS OF PYRIMIDO [4, 5-d] PYRIMIDINE DERIVATIVES

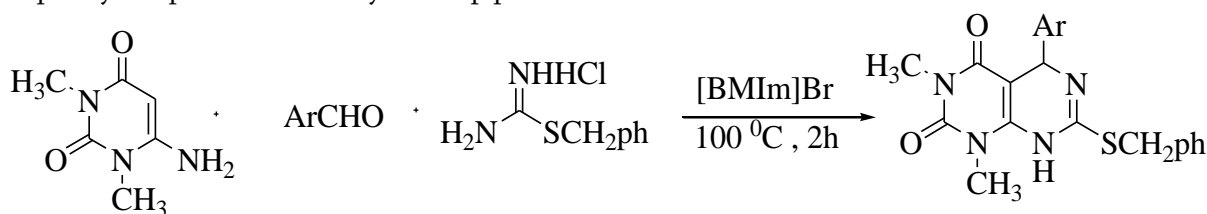
M. S. Shingare and Co-worker [13] have described an efficient, facile and solvent free synthesis of pyrimido [4, 5-d] pyrimidine by reaction of aromatic aldehyde, barbuteric acid and urea/thiourea using neutral alumina as energy transfer medium under non-

conventional microwave irradiation (MWI) (**Scheme-1**). In the optimization of reaction parameter, the reaction of benzaldehyde, barbuteric acid and urea was carried out with neutral alumina and without neutral alumina by varying microwave power from 150 watts to 150 watts and it was observed that excellent yield of desired product was obtained at microwave power 600 watts with solid support of neutral alumina under microwave irradiation. Excellent yield, short reaction time and high purity of product are the advantages of this method.



Scheme-1

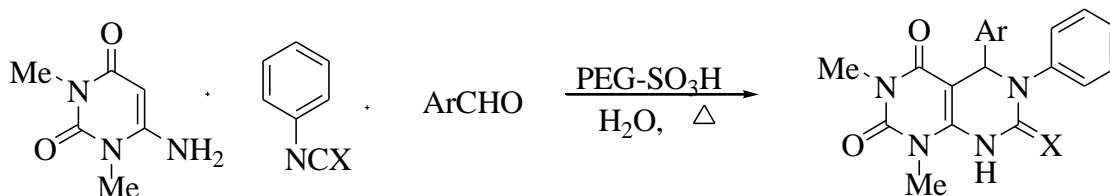
A. Bazgir and S. C. Azimi [14] have described a simple, novel, efficient and solvent free synthesis of pyrimido [4, 5-d] pyrimidine 2, 4, dione derivative through the reaction of 6-amino-1, 3-dimethyl uracil, aldehyde and 2-benzylisothioureia hydrochloride promoted by ionic liquid 1-butyl-3-methylimidazolium bromide ([BMIm] Br) (**Scheme-2**). In optimization of reaction condition temperature, solvent and type of ionic liquids were examined and it was observed that best result obtained with 6 mmol of [BMIm] Br at 100 °C. Further the generality of reaction condition was examined with aldehyde having electron withdrawing and electron donating group. Good yield was obtained in all cases. This method offer several advantages such as high yield, short reaction time, simplicity of operation and easy workup procedure.



Scheme-2

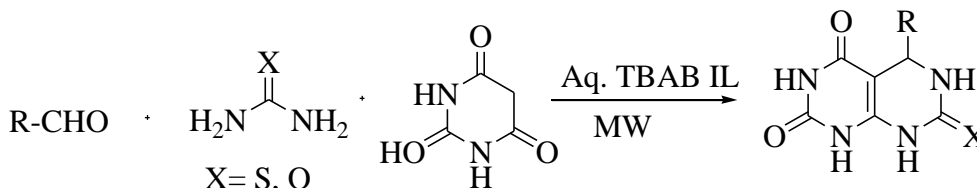
An efficient and regioselective synthesis of pyrimido [4, 5-d] pyrimidine derivative via multicomponent reaction of isothiocyanate aromatic, aldehyde and N, N-dimethyl-6-amino uracil in the presence of p-toluenesulfonic acid (p-TSA) as a Lewis acid catalyst in water reported by S. Majumder, and co-worker [15] (**Scheme-3**). Further the reaction was carried out using ortho and para substituted aromatic aldehyde gives moderate to good yield of product. It was observed that electron donating group at para position of aldehyde require less reaction time to give comparatively high yield of product while strong electron withdrawing group gave evidently poor yield. Lower yield of product was obtained with aldehyde having electron withdrawing or donating group at ortho position. No desired products were obtained with lower aliphatic aldehyde. Environmentally benign, inexpensive and economically feasible catalyst are the benefits of this procedure.

isothiocyanate and isocyanate with different aromatic aldehyde. It was observed that isothiocyanate gave lower yield when compared with isocyanate. The aromatic aldehyde having electron withdrawing group requires short time and gives high yield than those having electron donating group. Furthermore, recyclability of PEG-SO₃H catalyst was investigated. This method has several advantageous such as short reaction time, excellent yield, simple work up procedure and utilization of an inexpensive and reusable catalyst.



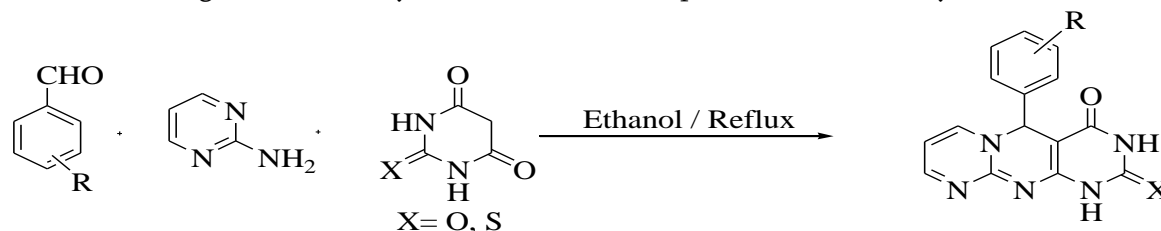
Scheme-6

An efficient microwave assisted and conventional synthesis of pyrimido [4, 5-d] pyrimidine derivative described by G. M. Bondle and S. T. Atkore [19] from three component condensation reaction of an aromatic aldehyde, urea/thiourea and barbuteric acid using aqueous tetra butyl ammonium bromide (TBAB) (**Scheme-7**). For the synthesis of pyrimido [4,5-d] pyrimidine an appropriate solvent was searched by examine the model reaction using different solvent like water, glycol, DMF, THF, ethanol, [Bmim]BF₄, [Bmim]Cl, [Bmim]PF₆ and tetra butyl ammonium bromide as solvent under microwave irradiation. It was found that using tetra butyl ammonium bromide as solvent reaction proceeded efficiently with high yield compare to other solvent. This reaction was also carried out under conventional heating method. It was observed that under microwave irradiation reaction proceed efficiently with high yield and short reaction time compare to conventional heating method.



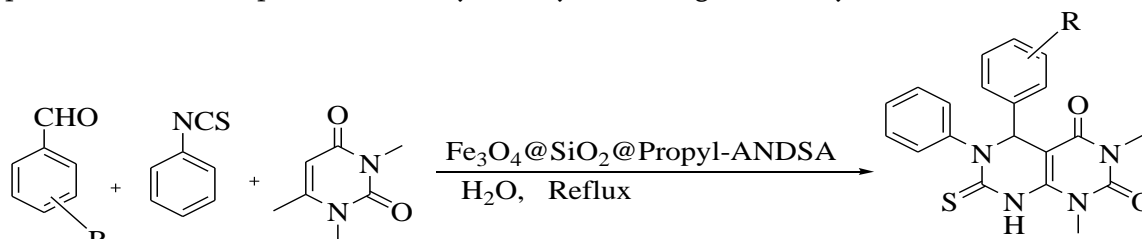
Scheme-7

P. V. Anbhule et al [20] have reported a convenient and uncatalyzed one pot three component synthesis of substituted dihyro-2H-dipyrimido[1,2-a, 4,5-d] pyrimidine-2,4(3H)-dione derivative by the reaction of barbuteric acid, aromatic aldehyde and 2-amino pyrimidine in ethanol under reflux condition (**Scheme-8**). In optimization of reaction condition, the effect of solvent was investigated on the reaction of 4-nitro benzaldehyde, barbuteric acid and 2-aminopyrimidine as model reaction using different solvent such as water, ethanol, acetonitrile, THF and DMF. It was found that the good to excellent yield was obtained in ethanol compared to other solvent. After optimization of reaction condition, different substituted aromatic aldehyde was investigated and it was observed that most of the substrate show suitable reactivity. This protocol offer several advantages such as catalyst free, clean reaction procedure, excellent yield and use of ethanol as solvent.



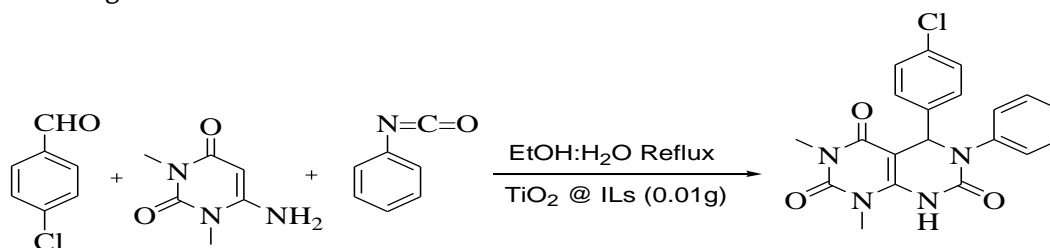
Scheme-8

R. Ghorbani-Vaghei and N. Sarmast [21] have reported a novel, simple, efficient and one pot multicomponent synthesis of substituted pyrimido[4, 5-d] pyrimidine using N, N-dimethyl-6-amino uracil, isothiocyanate and aromatic aldehyde catalyzed by Fe₃O₄@SiO₂@Propyl-ANDSA in water as solvent (**Scheme-9**). In optimization of reaction condition, the effect of catalyst loading, temperature and solvent were studied on the rates and yield of model reaction. Further the generality of these reaction conditions were examined by using different aromatic aldehyde having electron donating and withdrawing group. It was observed that the aromatic aldehyde having electron withdrawing group shows higher reactivity compare to aromatic aldehyde having electron donating group. Advantages of this method are use of heterogeneous Nano catalyst, high yield, simple work up procedure, ease of separation and recyclability of the magnetic catalyst and waste reduction.



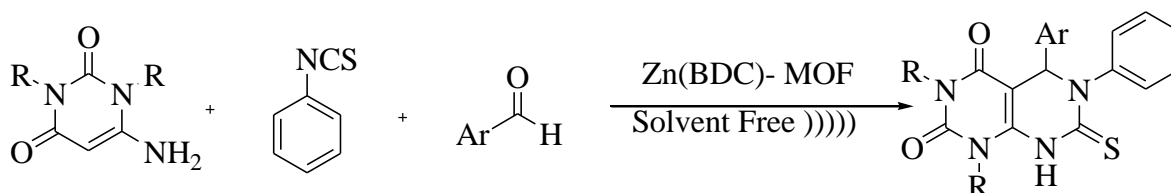
Scheme-9

R. Bakhshali-Dehkordi and Co-worker[22] have described the efficient synthesis of pyrimido [4, 5-d] pyrimidine derivative via one pot multicomponent reaction of phenylisocyanate, 6-amino N, N-dimethyl uracil and aromatic aldehydes using TiO₂ @ILs as a Nano catalyst (**Scheme-10**). In this method TiO₂ Nps were prepared by using beet juice extract and functionalized with ILs based on imidazole. The prepared catalyst was characterized by FT-IR, TGA, XRD, SEM and EDX. The reaction parameter such as solvent, amount of catalyst and temperature were optimized on reaction of 4-Cl-benzaldehyde, 6-amino N, N-dimethyl uracil and phenylisocyanate as model reaction. It was observed that the desired product of reaction was obtained when the reaction was performed in ethanol at 80 °C in the presence of TiO₂ @ ILs (0.01g). Further after optimization of reaction condition various aromatic aldehyde were investigated. It was found that all aromatic aldehyde gives excellent yield. The reusability of nano catalyst, short reaction time, simple workup and high yield are the advantages of this method.



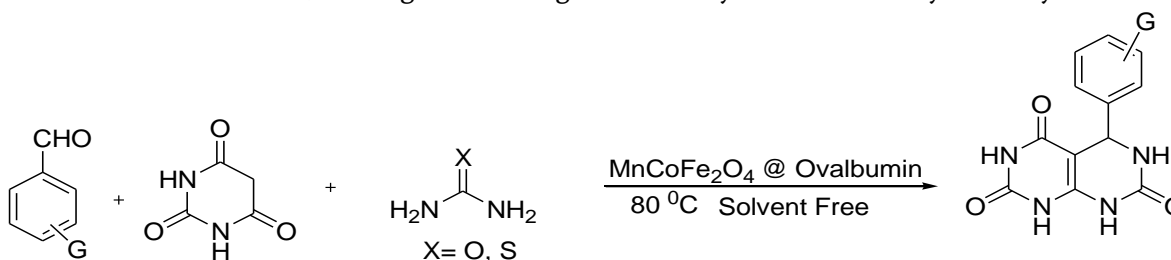
Scheme-10

M. H. Abdollahi-Basir et al [23] have successfully developed an efficient, solvent free procedure for the synthesis of pyrimido [4, 5-d] pyrimidine derivative by the condensation reaction of N, N-disubstituted-6-amino uracil, aromatic aldehyde and isothiocyanate using Zn(BDC)-MOF as heterogeneous catalyst under ultrasound irradiation (**Scheme-11**). The reaction parameter such as catalyst amount, ultrasound irradiation power and effect of solvent were examined on model reaction. After optimization of reaction condition the reaction was carried out using different aldehydes. It was found that the desired products of reaction were obtained with high yield in short reaction time. This protocol has several advantages such as green and cost-effective procedure, reusability of catalyst, high isolated yield, ease of the preparation and short reaction time.



Scheme-11

A. Mobinikhaledi and Co-worker [24] used $\text{MnCoFe}_2\text{O}_4@$ ovalbumin nanoparticle catalyst for the synthesis of pyrimido [4, 5-d] pyrimidine derivative via multicomponent reaction of aldehyde, barbuteric acid, urea or thiourea under solvent free condition (Scheme-12). The $\text{MnCoFe}_2\text{O}_4@$ ovalbumin nano particle was synthesized using $\text{MnCoFe}_2\text{O}_4$ MNPs and egg white nano-ovalbumin and characterized by FT-IR, SEM, thermogravimetric and vibrating sample magnetometer. In optimization of reaction condition solvent, catalyst amount, temperature and solvent free condition were investigated on model reaction of 4-Cl benzaldehyde, urea and barbuteric acid. The best reaction condition was observed that solvent free condition using 10 mg of MNPs at 80 °C. After optimization of reaction condition, various aldehyde having electron withdrawing and electron donating group was investigated. It was observed that the reaction proceeds more effectively and desired product were obtained with good yield with aldehyde having electron withdrawing group compared to aldehyde having electron donating group. The main advantages of this method are short reaction time, high yield, and solvent free condition, use of green heterogeneous catalyst and reusability of catalyst.



Scheme-12

III. CONCLUSION

This review is a compilation of recent synthetic strategies reported for the synthesis of pyrimido [4, 5-d] pyrimidine derivatives during the period 2009 to 2023. This literature survey shows that the pyrimido [4, 5-d] pyrimidine derivatives are easily to be synthesized from various starting materials. We believe that the present review can be used as a source of advanced information related to different method used for the synthesis of pyrimido [4, 5-d] pyrimidine derivatives. This could be useful to organic chemist, researcher and students in their research work.

IV. REFERENCES

- [1]. S. M. El-Moghazy, D. A. Ibrahim, N. M. Abdelgawad, N. A. H. Farag, A. S. EL-Khouly, *Sci. Pharm.*, 2011, 79, 429.
- [2]. E. M. Grivsky, S. Lee, C. W. Sigel, D. S. Duch, C. A. Nichol, *J. Med. Chem.* 1980, 23, 327.
- [3]. J.P. De la Cruz, T. Carrasco, G. Ortega, F. Sanchez De la Cuesta, *Lipids*, 1992, 27, 192.
- [4]. H. El-Subbagh, S. M. Abu-Zaid, M. A. Mahran, F. A. Badria, and A. M. Al-Obaid, *J. Med. Chem.*, 2000, 43, 2915.
- [5]. S. R. Kanth, G. V. Reddy, K. H. Kishore, P. S. Rao, B. Narsaiah, U. S. N. Murthy, *Eur. J. Med. Chem.*, 2006, 41, 1011.
- [6]. N. Kitamura, A. Onishi, EU Patent 163599; *Chem. Abstr.* 1984, 104, 186439.

- [7]. E. P. Falcao, S. J. Melo, R. M. Srivastava, M. T. J. A. Catanho, S. C. Nascimento, Eur. J. Med. Chem., 2006, 41, 276.
- [8]. L. R. Bennet, C. J. Blankley, R. W. Fleming, R. D. Smith, D. K. Tessman, J. Med. Chem., 1981, 24, 382.
- [9]. V.J. Ram, A. Goel, S. Sarkhel, P.R. Maulik, Bioorg. Med. Chem. 2002, 10, 1275.
- [10]. G.W. Rewcastle, A.J. Bridges, D.W. Fry, J.R. Rubin, W.A. Denny, J. Med. Chem. 1997, 40, 1820.
- [11]. D.W. Fry, M.A. Becker, R.L. Switzer, Mol. Pharmacol. 1995, 47, 810.
- [12]. J. E. Gready, C. McKinlay, M. G. Gebauer, Eur. J. Med. Chem. 2003, 38, 719.
- [13]. A. H. Kategaonkar, S. A. Sadaphal, K. F. Shelke, B. B. Shingate, M. S. Shingare, Ukrainica Bioorganica Acta, 2009, 1, 3.
- [14]. A. Bazgir, S. C. Azimi, Iran. J. Catal., 2013, 3, 21.
- [15]. S. Majumder, P. Borah, P. J. Bhuyan, Tetrahedron Lett. 2014, 55, 1168.
- [16]. Z. D. Fang, D. Fang Y. Y. Tan, Res. Chem. Intermed., 2015, 41, 1203.
- [17]. A. Mobinikhaledi, T. Mosleh, N. Foroughifar, Res. Chem. Intermed. 2015, 41, 2985.
- [18]. S. Badvel, R. R. Gopireddy, T. B. Shaikh, S. Hasti, V. R. Tummaluru, N. R. Chamarthi, Chem. Heterocycl Compd, 2015, 51, 749.
- [19]. G. M. Bondle, S. T. Atkore J. Chem. Pharm. Res. 2016, 8, 717.
- [20]. P. T. Patil, P. P. Warekar, K. T. Patil, D. K. Jamale, G. B. Kolekar, P. V. Anbhule, Res. Chem. Intermed., 2017, 43, 4103.
- [21]. R. Ghorbani-Vaghei, N. Sarmast, Appl. Organomet. Chem. 2018, 32, 1.
- [22]. R. Bakhshali-Dehkordi, M. A. Ghasemzadeh, J. Safaei-Ghomi, J. Mol. Struct., 2020, 1206, 127688.
- [23]. M. H. Abdollahi-Basir, F. Shirini, H. Tajik, M. A. Ghasemzadeh, Polycycl. Aromat. Compd., 2021, 41, 1580.
- [24]. A. Mobinikhaledi, N. Ahadi, F. S. Hoseini, F. Sameri, Res. Chem. Intermed., 2023, 49, 3501.

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