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Review Article

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A Systematic Review on Advances in Synthesis of Dihydropyrimidin-imines

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Abstract
The dihydropryimidin -imines are having wide range of biological activities. The synthesis of potential substituted dihydropryimidin -imines by different methods among them the major ones are microwave irradiation, phase transfer catalyst and using biocatalyst. The comparison of these methods to get an efficient and ecofriendly way for synthesis of bigenelli dihydropryimidin -imines. The different study shows different catalyst used for the efficient synthesis of dihydropryimidin -imines. The one pot synthesis was also studied in comparison with microwave irradiation and phase transfer catalyst. Among them usage of biocatalyst was found not only efficient and eco-friendly but also short reaction time. This review focus on synthesis methods which is environmentally safe and less time consuming with minimum quantity of reagents.

Keywords: Dihydropryimidin -Imines, Microwave Irradiation, Phase Transfer Catalyst, Biginelli reaction

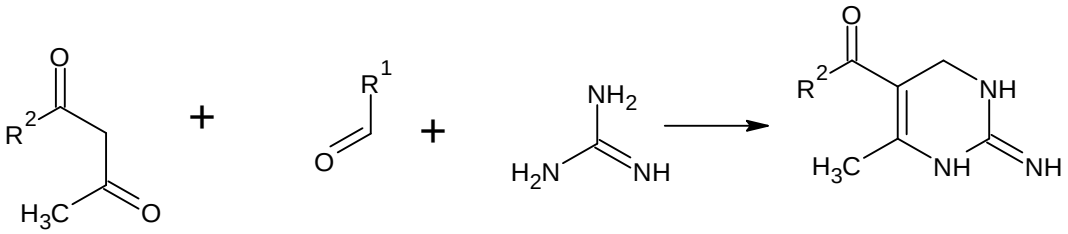
Introduction

Dihydropyridimines are a type of chemical compounds having pyrimidine rings that have two hydrogen atoms on one of the carbon atoms, giving them a reduced form of pyrimidine. Due to their adaptable chemical structure and a range of pharmacological actions, these compounds are of great interest in the domains of chemistry and pharmacology [1].

Different methods are widely used to synthesis Dihydropyrimidines, among the methods we used microwave irradiation, phase transfer catalysis and biocatalyst methods. The comparison of these methods to get an efficient and ecofriendly way for synthesis of bigenelli dihydropryimidin -imines. Microwave irradiation method has of plus of rapid and even heating. It is a good option for many procedures since it can dramatically shorten reaction times when compared to traditional heating techniques.it has many benefits like energy saving, high yield results, green chemistry and versality [1.] In phase transfer catalysis method, they can speed up reactions between immiscible phases, increase yields, and provide a variety of useful and advantageous effects, phase transfer catalyst techniques are important tools in organic synthesis. Enzymes and other biological molecules are used as catalysts in chemical reactions through a process called biocatalysts. The capacity of biocatalysts to selectively catalyze processes under benign conditions, such as at low temperatures and pH levels, is one of its key benefits. This makes it an eco-friendlier substitute for conventional chemical synthesis techniques, which frequently call for difficult conditions and generate waste. Economic benefits of biocatalysts include cheaper production costs and the ability to synthesize complex compounds that are challenging to make using other techniques [5].

Review of Literature

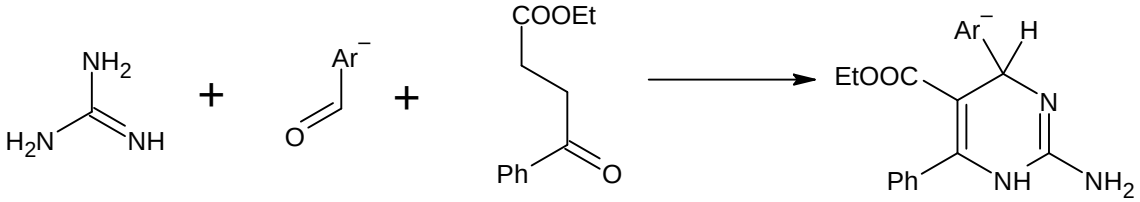
1. Bais *et al* (2020) [2] conducted a study on One Pot Synthesis of Micromolar BACE-1 Inhibitors Based on the Dihydropyrimidinones Scaffold and Their Thia and Imino Analogues. They prepared the imine derivatives through Biginelli reaction from guanidine hydrochloride using different aldehydes and β-dicarbonyl compounds. They synthesize imine derivatives by irradiating appropriate ethanolic solution of aldehydes with β - Ketoester and guanidine at 120ºC for 10min. after it subsides to room temperature cold water was added and maintained the mixture at 5ºC. The product was washed and triturated or recrystallized. The products were evaluated for their In vitro β – secretase inhibitory activity and found to be active.



Scheme 1: Bigenelli synthesis by microwave irradiation

R1	R2	Percent yield (%)
Benzyl	Ethyl	83
Benzyl	Methyl	80
Fluoro benzyl	Ethyl	70
1-Naphthyl	Ethyl	88
2-Naphthyl	Ethyl	90
Benzyl	Benzyl	47

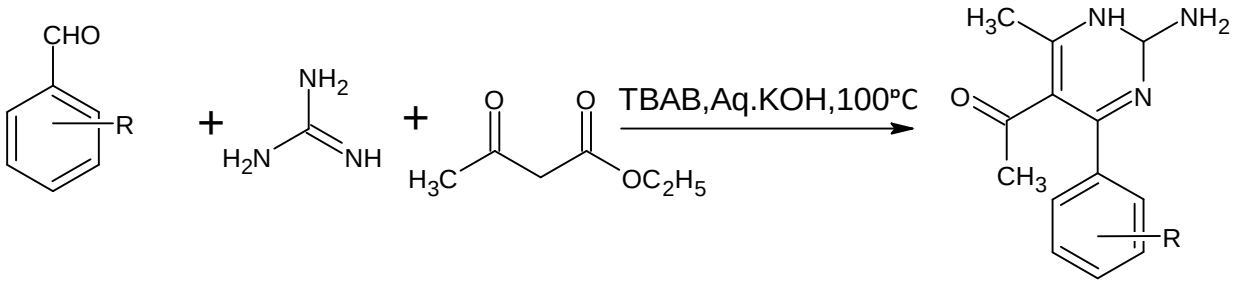
2. Eynde *et al* (2020) [3], had done the regioselective synthesis of novel pyrimido[1,2-a] pyrimidines. They used DMF for the imine synthesis. The aldehyde, ethyl benzoyl acetate, guanidine and sodium hydrogen carbonate were reacted at 70ºC for 3 hours in presence of DMF.



Scheme 2 : synthesis using DMF

Ar	Ph	Percent yield (%)
Benzyl	Ethyl benzoyl	75
Methyl Benzyl	Ethyl benzoyl	85
Methoxy benzyl	Ethyl benzoyl	75
Chloro benzyl	Ethyl benzoyl	85

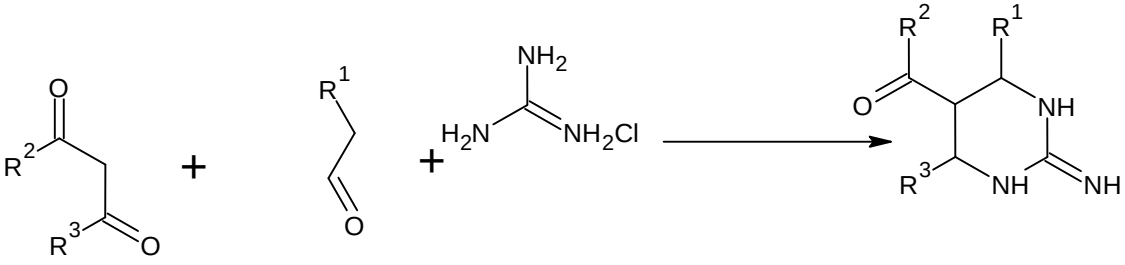
3. Bahar *et al* (2008) [4] synthesized 3,4-dihydropyrimidin-2(1H)-imines from substrates of different aromatic aldehydes. Ethyl acetoacetate and guanidine. The best yield was obtained through the ratio of 1:1:1: 1:0.15 of beta keto ester, aldehyde, guanidine and TBAB as catalyst. The use of TBAB increased the yield and reduced the reaction time.



Scheme 3: synthesis via phase transfer catalyst

R	β - Ketoester	Percent yield (%)
H	Ethyl acetoacetate	92
4-Methyl	Ethyl acetoacetate	89
2,3,4-Trimethoxy	Ethyl acetoacetate	87
3,4 - Dimethoxy	Ethyl acetoacetate	89
4-N,N-Dimethyl amino	Ethyl acetoacetate	94

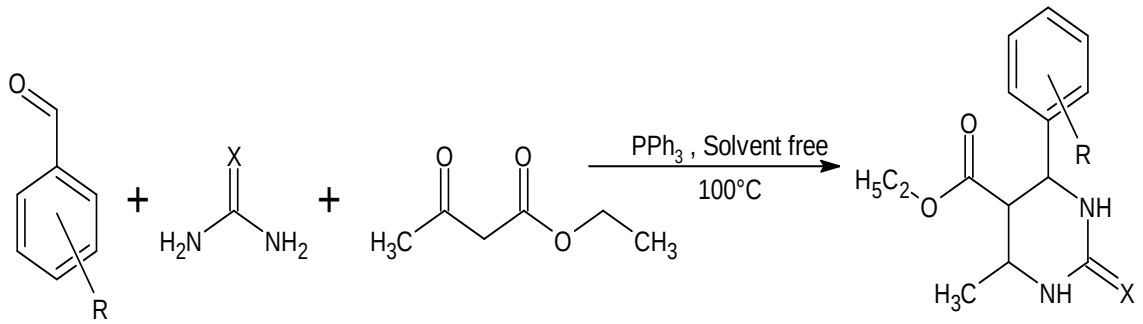
4. Felluga *et al* (2018) [1], did an efficient synthesis of 2-amniodihydropyrimidines under microwave irradiation. The two fold excess of guanidine hydrochloride in presence of alcohol at 120°c will give high yield with shorter reaction time. The reaction of β – keto ester, secondary or tertiary β – keto amides and 1,3 – diketones are also compatible for this method. They have synthesized a set of 26, 2-amino-3,4-dihydropyrimidines. The microwave irradiation avoids the prolonged heating and high boiling solvents. They optimized the conditions of reaction and obtained best results with ethanol. They have varied the temperature of reaction with ethanol and found out that the best condition for Biginelli reaction with guanidine hydrochloride, Benzaldehyde and ethyl acetate is 120°c for ten minutes. Among them, the derivatives with high yield in ethanol is given in the table



Scheme 4: synthesis by MWI

R1	R2	R3	Percent yield (%)
4-FC_6H_4	OEt	Me	91
Ph	O-t-Bu	Me	81
4-$BnOC_6H_4$	OEt	Me	82
1-Naphthyl	OEt	Me	80
Ph	Me	Me	85

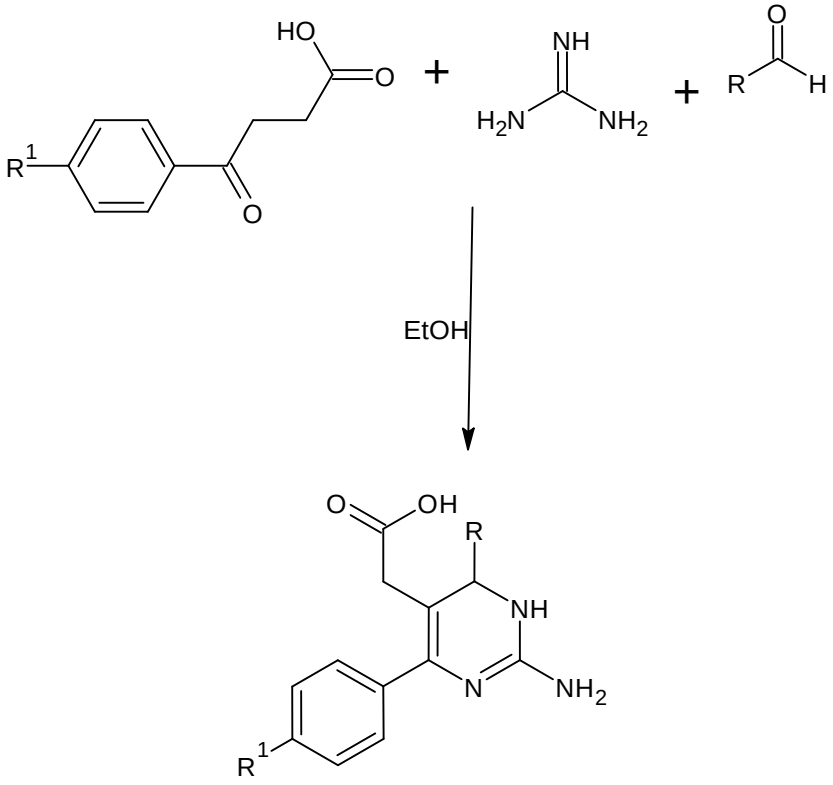
5. S. Sheik Mansoor *et al* (2011) [6], prepared dihydropyrimidin-imines under solvent free condition via a lewis base. They were synthesized by modified Biginelli cyclocondensation reaction which was catalyzed by triphenylphosphine as lewis base. The use of catalyst improved the reaction rate and yield with reduced time. Along with that, KOH (Bronsted base) was also found effective when replaced the Lewis acids. The substituted dihydropyrimidinones/thiones /imines were prepared and the table below shows the dihydropyrimidinimines synthesized.



Scheme 5: Synthesis using catalyst

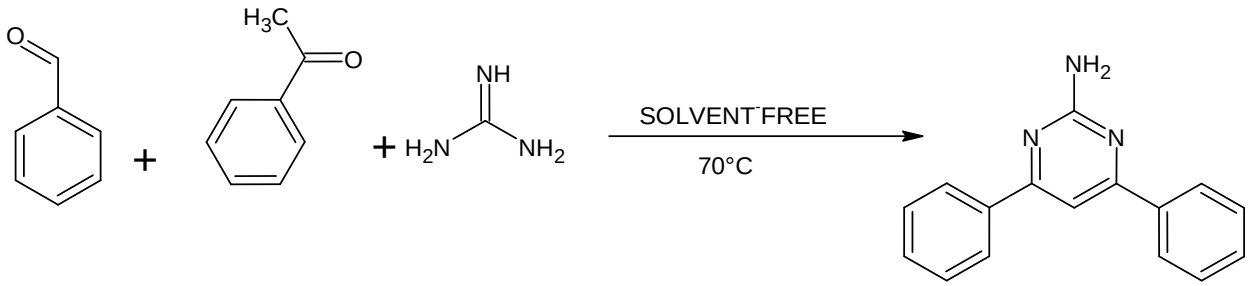
R	Percent yield (%)
H	84
4-Methyl	90
2,3,4 – Trimethoxy	84
4-Methoxy	82
4-N,N-dimethyl amino	80
3-Chloro	80

6. Bahekar *et al*(2003)[7], synthesized and studied anti-inflammatory activity of [2-amino-6-(4-substituted aryl)-4-(4-substituted phenyl)-1,6-dihydropyrimidine-5-yl]-acetic acid derivatives by base catalysed condensation of guanidine nitrate, β-aroylpropanoic acid and aromatic aldehyde. The mixture of components were refluxed in oil bath and recrystallized with suitable solvents. The yield was good for phenyl and p-substituted halogen derivatives. The anti-inflammatory activity was compared in reference with diclofenac sodium. They showed remarkable reduction in the inflammation.



Scheme 6: Synthesis using catalyst

7. Zhuang *et al* (2009)[11], Prepared 2-Amine-4,6 diaryl pyrimidine by three componentreaction under solvent free condition in the presence of sodium hydroxide. It provided greater selectivity , increased reaction rate, and simplicity. The Multicomponent condensation of aromatic ketones, aldehydes and guanidine carbonate by heating for 25min. the yield was high and they prepared chalcones using correspondimg aldehydes and ketones and used it to react with guanidine carbonate which showed a very low yield. The cyclocondensation protocol for the synthesis was easy as the availability of the reagents and good yields, it also avoids organic solvents.



Scheme7: Synthesis under solvent free condition

Conclusion

The review of literature highlights significant advances in the synthesis of various dihydropyrimidine-imines derivatives and their analogues. The microwave irradiation method provided faster rection with high yield, the regioselective approach through use of DMF showed high efficiency. The phase transfer catalyst methods showcased enhancing yield and reduced reaction time and also the solvent free method offered an environmentally friendly approach for synthesis. All these studies indicate the versatility and potential of dihydropyrimidine-imine derivatives and these diverse synthetic approaches provide valuable methodologies for future research and development.

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