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Dihydropyrimidinone Synthesis and Pharmacological Action – An Overview

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ABSTRACT

3,4-Dihydropyrimidinones are classified as six-membered heterocyclic compounds with a pyrimidine ring that has two nitrogen's as heteroatoms and two keto groups-one on the ring and one at the α position relative to the ring. The molecule exhibits diverse biological activities due to the presence of keto groups and pyrimidine rings in its structure. Biginelli three component reactions are mostly used in the production of dihydropyrimidinone. The yield of the traditional Biginelli reaction is frequently low and needs a long reaction time. In this case, the focus is on different synthetic reactions that have been tweaked to produce 3, 4-Dihydropyrimidinones and their uses.

INTRODUCTION

Almost one-third of modern publications are in the field of heterocyclic chemistry, which is a significant subfield of organic chemistry [1]. The importance of heterocyclic molecules in our biological system is crucial. They are an essential component of numerous natural products, nucleic acids, and pharmacologically active compounds. Heterocyclic substances like purine, pyrimidine, etc. are also composed of the base pair of DNA and RNA, which is guanine, cytosine, adenine, and thymine. Numerous therapeutic candidates, including those with anticancer, antibiotic, anti-inflammatory, antidepressant, antimalarial, anti-HIV, antimicrobial, antibacterial, antifungal, antiviral, antidiabetic, herbicidal, fungicidal, and insecticidal properties, also contain heterocyclic compounds [2]. Certain naturally occurring compounds with strong biological activity against certain diseases have been found. For example, quinine is utilised as an antimalarial medication, and vinblastine and vincristine are employed as anticancer agents.

The most significant heterocyclic moiety is the pyrimidine. In medicinal chemistry, pyrimidine derivatives are used in many different therapeutic contexts. The presence of a pyrimidine base in thymine, cytosine, and uracil—essential building components of nucleic acids, DNA, and RNA—is one theory as to why they are active [3]. Many compounds with pyrimidine as the core nucleus were created and tested for their antihypertensive, anticancer, antimicrobial, antihyperglycemic, antiarrhythmic, anti-inflammatory, analgesic, antibacterial, anti-HIV, and antitubercular properties [4, 5, 6, 7, 11, 12]. Owing to the numerous medicinal benefits, scientists are drawn to creating novel dihydropyrimidine compounds. Dihydropyrimidinones are tiny, incredibly beneficial compounds with a wide range of therapeutic uses. They have a chemical formula of C4H6N20 and exhibit a wide range of biological activity. The heterocyclic moiety has two N-atoms positioned at positions 1 and 3. They are derivatives of pyrimidines with an extra ketone group.

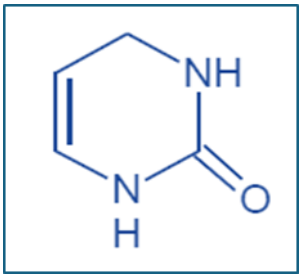
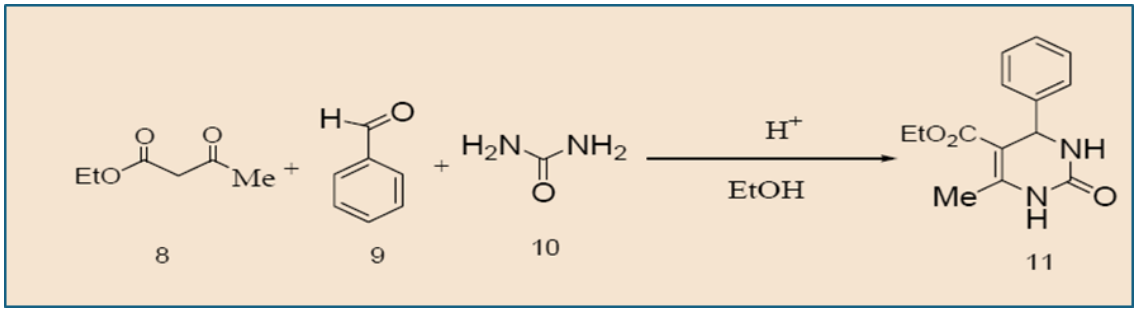


Figure 1: Structure of 3,4-dihydropyrimidin-2(1*H*)-one

SYNTHESIS OF 3, 4-DIHYROPYRIMIDINONE

Biginelli originally published the most straightforward and widely used technique for synthesising 3, 4-Dihydropyrimidinone in 1983. [13] The condensation reaction combining benzaldehyde, ethylacetoacetate, and urea/thiourea is a one-pot reaction consisting of three components. The Biginelli reaction is the name given to this reaction. In addition to needing a longer reaction time-roughly 20 hours—the traditional Biginelli reaction also produces poor yields for some aldehydes. [14] Because it was the most straightforward approach, scientists studied the reaction and created a number of modified procedures for the traditional Biginelli reaction that have a faster reaction time and a higher product yield. [13, 15] The only new adjustments are the reaction conditions, reagent derivatives, and specific catalysts; the basic reagents stay unchanged. According to the published research, these altered procedures outperform the traditional Biginelli reaction in terms of product yield while requiring a shorter reaction time.

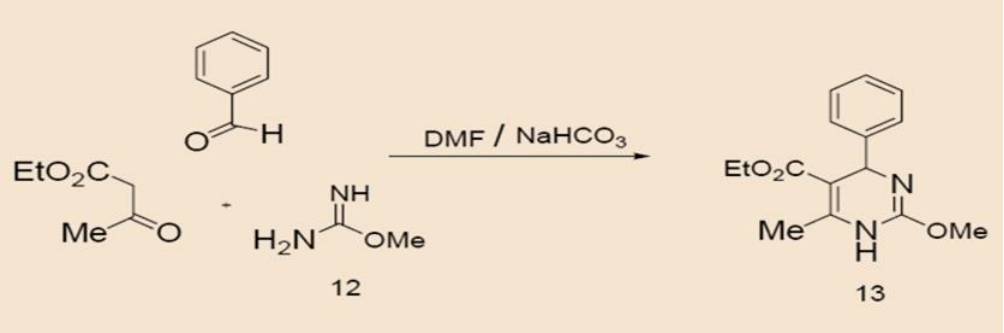
P. Bigenelli published a study in 1893 on the urea (10), benzaldehyde (9), and ethyl acetoacetate (8) acid catalysed cyclo-condensation reaction. The three components were dissolved in ethanol, and a catalytic quantity of hydrochloric acid was heated to reflux temperature to initiate the reaction. 3,4-dihydropyrimidin-2(1H)-one (11) is the result of this unique one-pot, three-component synthesis, which is also known as the "Biginelli reaction," "Biginelli Condensation," or "Biginelli dihydropyrimidine synthesis." It precipitated upon cooling the reaction mixture. [16] **(Scheme-1)**.



Scheme-1

Since then, several enhanced versions have appeared, utilising new catalysts, reagents, techniques, and methods. There have been numerous documented synthetic methods for creating these molecules using PPE, KSF clay, [17] H_2SO_4, [18] $Bi(OTf)_3$, [19] LiBr, [20] $InCl_3$, [21] lanthanide triflate, [22] $FeCl_3$, [23] $CdCl_2$, [24] BF_3•OEt_2, [25] $LaCl_3$, [26] ceric ammonium nitrate (CAN), [27] ion-exchange resin, [28] $BiCl_3$, [29] $Mn(OAc)_3$, [30] $InBr_3$,

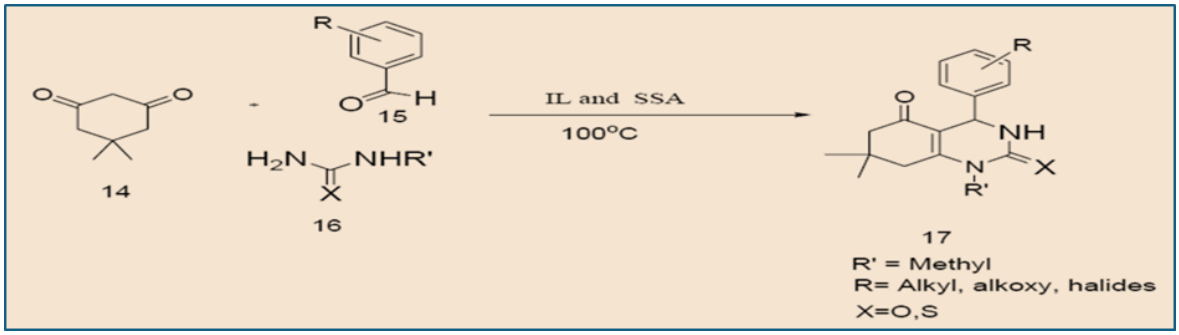
[31] NH_4Cl, [32] $SiO_2/NaHSO_4$, [33] $LiClO_4$, [34] $ZrCl_4$, [35] 1-n-butyl-3-methyl imidazolium tetrafluoroborate, [36] ytterbium triflates, [37] $Cu(OTf)_2$, [38] $SnCl_2.2H_2O$, $AlCl_3/KI$, $CoCl_2$ /$MnCl_2$, $AlCl_3/AlBr_3$, [39a-d] P_2O_5, [40] $BiOClO_4.xH_2O$, [41] $CaCl_2$, 1,3-Dibromo-5,4-dimethylhydantoin, zinc tetrafluoroborate. [42a-c] Kappe reported the synthesis of 2-methoxy-1,4-dihydropyrimidines **(13)** which was obtained by condensation of ethylacetoacetate, O-methylisourea **(12)** and an appropriate aldehyde. [43] **(Scheme-2)**.



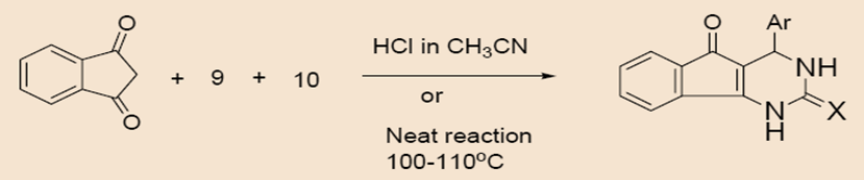
Scheme-2

Common open-chain β-dicarbonyl molecules have recently been expanded to include cyclic β-diketones, β-ketolactones, cyclic β-diesters or β-diamides, benzocyclic ketones, and α-ketoacids with the purpose of creating innovative Biginelli-like scaffold syntheses. By reacting 5,5-dimethyl-1,3 cyclohexanedione 14 and aldehydes 15 with urea (16), Nmethylurea, or thiourea (16) using 1-butyl-3-methylimidazolium bromide [bmim]Br as an ionic liquid (IL) in combination with a solid acid catalyst, silica sulfuric acid (SSA), Shabani et al. created the biginelli type (17) compound. [44] (Scheme-3).

In the previous report by Perumal et al., ionic liquid in SSA was substituted with HCl in acetonitrile, and indane-1,3-dione (18) was used to yield 4-arylindeno-[l,2-d] pyrimidine (19). It was discovered that a solvent-free and catalyst-free reaction at 100–110 °C produced a better yield than those catalysed by HCl. (Scheme- 4).



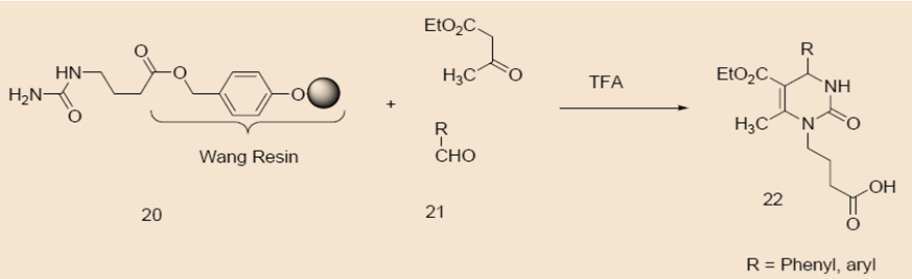
Scheme-3



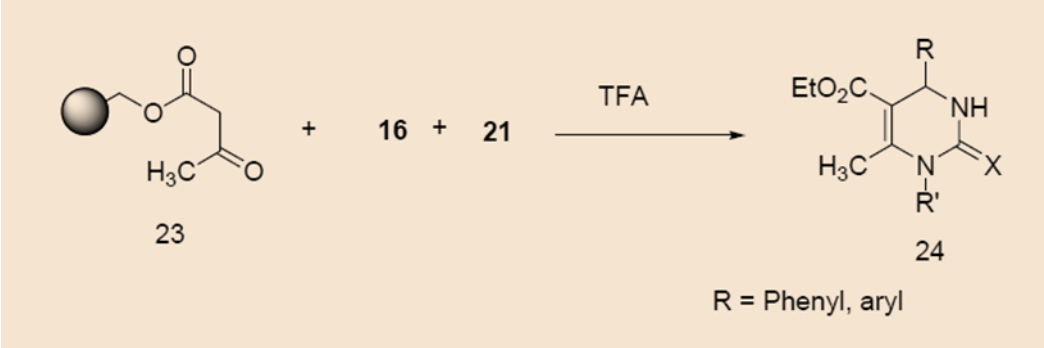
Scheme-4

The automated microwave-assisted synthesis of dihydropyrimidines using Yb(OTf)3 was described by Kappe et al. [45] In a 12-hour period, they created a library of 48 chemicals, which includes a range of carbon acids, N-substituted ureas, and aldehydes. A different route to a wide range of dihydropyrimidines was via solid-phase synthesis. High yield products were obtained via solid-phase synthesis by using a substantial excess of reagents. Furthermore, the easily washable by-products that were not resin bound removed the need for additional filtration. Numerous polymer-supported building blocks have been investigated, such as the linker's attachment to the urea and β-keto ester constituents. The first instance of a solid-phase Biginelli reaction utilising resin-bound urea was shown by Wipf et al. (Scheme 5a). [46] The N-1 substituted products were obtained by cleaving the resin with TFA and forming the dihydropyrimidine.

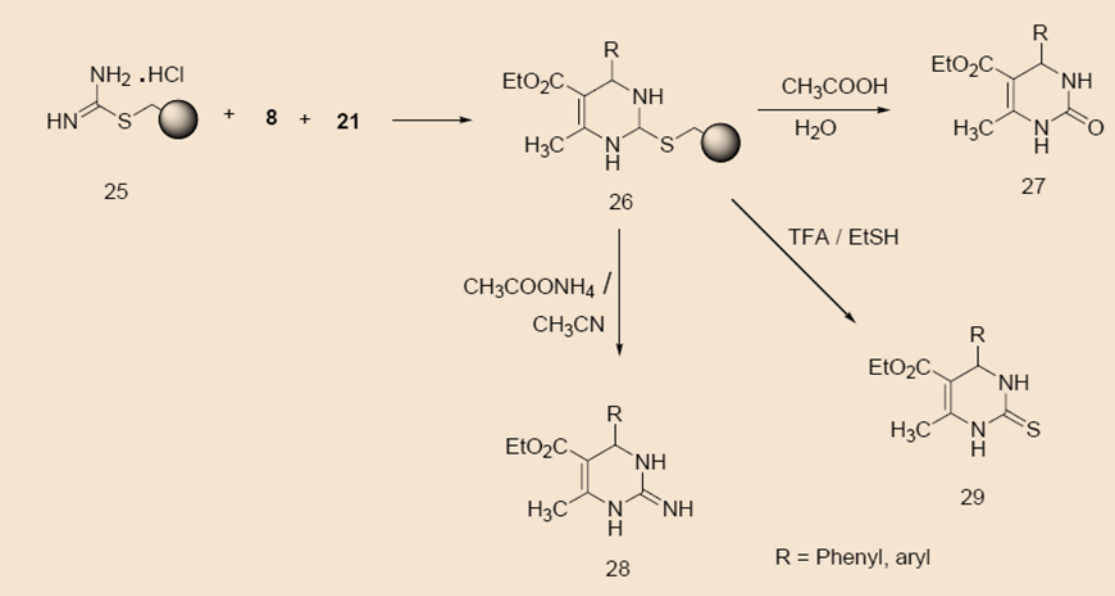
Using an immobilised β- keto ester reagent 23, Kappe et al. expanded on the solid-phase application's breadth (scheme 5b). [47] When the resin was broken down using this method, S-carboxylic acid dihydropyrimidines 24 and N-1 unsubstituted compounds were produced. Kappe also used the polymer-bound thiuronium salt 2540 (Scheme 5c) in another application. Following the Biginelli reaction's conclusion, the resin-bound dihydropyrimidines were broken down under various circumstances to produce 2-iminodihydropyrimidines (28), thiopyrimidines (39), or dihydropyrimidines (27). Numerous dihydropyrimidines can be synthesised using these solid-phase techniques with excellent yields, great purity, and even automation potential.



Scheme-5a

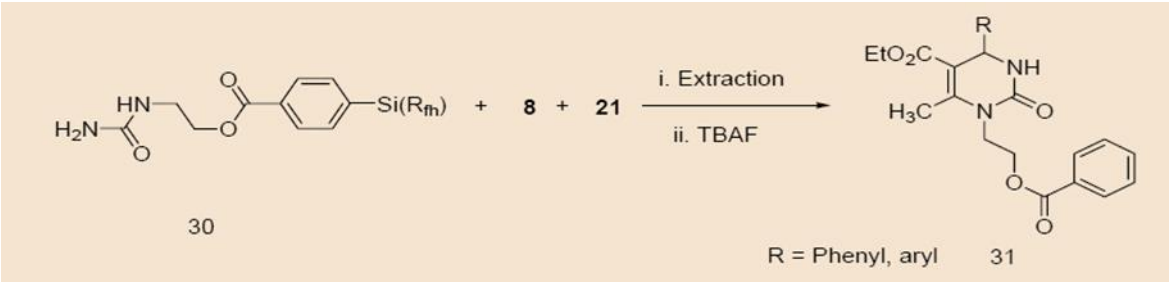


Scheme-5b



Scheme-5c

Fluorous-phase chemistry was modified by Curran et al. [48] to synthesise dihydropyrimidines. These tactics rely on the strong capacity of fluorinated chemicals to combine with solvents that have undergone fluorination. Since the by-products were insoluble in the fluorinated solvent, the reaction mixture was refined using a liquid-liquid extraction technique. Fluorinated ureas 30, which Curran synthesised, were extracted cleanly into fluorinated hexanes after undergoing the Biginelli reaction. The result of desilylation is N-1 substituted dihydropyrimidines (31). The fluorous-phase reaction yields are similar to those of reactions carried out in accordance with Biginelli reaction conditions (Scheme-6). Nevertheless, the fluorous approach necessitated the use of costly fluorinated solvents and the production of fluorinated ureas.



Scheme-6

APPLICATION:

1. Derivatives of dihydropyrimidinone have garnered a lot of synthetic attention due to their known calcium antagonistic effect [50] in the cardiovascular systems. Calcium antagonists reduce the force of cardiac muscle contraction by blocking the entry of calcium ions via plasma membrane channels, which dilates vascular smooth muscle. Certain calcium antagonists have been utilised as hypertension medications, including verapamil and nifedipine. Nevertheless, there is a significant drawback to using verapamil plus nifedipine to treat hypertension. These medications require repeated administrations to achieve sufficient clinical efficacy due to their very short plasma half-lives, which also decreases patient compliance. Consequently, dihydropyrimidines, which are appropriate for calcium antagonists with strong and sustained vasodilative, hypotensive, or antihypertensive action, took the place of the previously listed medications. [51]

2. Pyrimidines have a well-established biological relevance since they are considered favoured molecules with a broad range of biological activity, including antiviral and anticancer properties. AZT, DDI, and DDC are examples of therapeutically significant antiretroviral drugs that include the pyrimidine la scaffold. According to Biginelli's first study, another similar structure of the lb type is likewise extremely easily accessible by MCR using urea, active methylene compounds, and aldehydes in the presence of a catalyst. Due to its broad pharmacological profile, which includes alpha-agonists, calcium channel blockers, and antihypertensive agents (which can be thought of as aza analogues of clinically used medications like niguldipine, felodipine, and nifedipine), type lb pyrimidine scaffolds have been the subject of extensive research in recent years. [52]

3. The natural marine alkaloids batzelladine A and B, which are the first low molecular weight natural compounds to prevent HIV gp 120 from attaching to CD4 cells and may have therapeutic promise for AIDS, also include the DHPM unit.

4. By changing the substituents in almost all six places of the pyrimidine nucleus, Parlato et al. were able to synthesise a variety of dihydropyrimidinone derivatives with intriguing action against the Sendai virus, HIV, and Rubella virus. In addition to these, substituted pyrimidine derivatives have been employed as calcium channel blockers, neuropeptide y-antagonists, α-l a-antagonists, antihypertensive drugs, anticancer medications (Monastrol), antimalarial agents, and anti-inflammatory compounds. [53]

CONCLUSION

Since its discovery in 1893, the Biginelli dihydropyrimidine MCR has advanced significantly. The Biginelli MCR has been successfully adapted to the demands and expectations of modern organic chemistry, starting with the preparation of simple pyrimidine heterocycles in the late 19th century and continuing through the creation of targeted compound libraries of biofunctional DHPMs and the enantioselective total synthesis of complex natural products. Combinatorial synthesis and high-throughput screening approaches will surely lead to the discovery of novel dihydropyrimidines with significant biological effects due to the pharmacological potency of the DHPM scaffold. Thus, the Biginelli reaction has a bright future in the twenty-first century.

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