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Stereochemistry of Dihydropyrimidinones Derivatives Synthesized by Brick Dust Catalytic Reaction

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Abstract

A number of catalytic synthetic reactions have been reported which play the important role in stereochemistry of compounds. The key to the success of this protocol was the generation of stereogenic centers in 1, 4-Dihydropyrimidinones (DHPMs) and the influence of catalysts on their configuration. Waste brick dust was found to be an effective catalyst, generating chiral DHPMs derivatives using aryl aldehyde, urea, and ethyl acetoacetate. This work mainly focuses on the stereochemistry of brick-dust catalyzed DHPMs derivatives. Discovery of brick dust catalyst associated with several benefits such as rapid clean reaction, simple, and ease work-up.

Keywords: Biginelli reaction, Brick dust, Stereochemistry

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Introduction

Dihydropyrimidinones (DHPMs) is a nitrogen-containing heterocyclic nucleus that was first discovered by Pietro Biginelli in 1893.[1] The Biginelli reaction is a three-component cyclo condensation reaction between substituted or unsubstituted aldehyde, urea, and 1,3-dicarbonyl compound resulting in the formation of 1,4-DHPM derivatives.[2] Pyrimidines have made significant progress in their development over the past many decades and their derivatives have gained attention for their broad range of biological applications.[3] Series of FDA-approved pyrimidine derivatives with their commercial products such as imatinib,[4] nilotinib,[5] dasatinib,[6] sulfadiazine,[7] and rosuvastatin[8] are available in market [Figure 1]. Very recently, DHPMs derivatives have emerged as a β-glucuronidase inhibitors,[9] calcium channel blockers,[10,11] anti-bacterial,[11] anti-fungal,[12] anti-cancer,[13,14] anti-viral,[15] anti-inflammatory,[16] anti-malarial agents,[17] anti-hypertensive,[18] and α1-adrenergic antagonists agents.[19]

A catalyst acts as an important tool for the study of organic molecules, catalyzing a diverse range of synthetic transformations. In 2021, the Nobel prize in chemistry was awarded to Benjamin List[20] and David W.C. MacMillan,[21] for their discovery of organocatalysis. The heterogeneous catalyst plays a crucial role in the stereochemistry of compounds. For example, with a palladium catalyst, alkyl electrophiles show stereospecificity and inversion of the stereogenic center, while with a nickel catalyst, alkyl halides show racemization of electrophilic carbon.[22]

Recently, metal oxides are used as a catalyst in several organic reactions but their cost is an important factor affecting the total production of final product,[23-26] Brick dust contains dominantly metal oxides such as SiO_2, Al_2O_3, CaO, and MgO in variable proportions,[27-30] These oxides are known for their ability as dehydrating agents. Ceramic residue like brick dust can be used to synthesize bioactive molecules and their intermediates with a faster rate, a shorter time, a higher yield, and great selectivity. The stereochemical aspects of DHPMs are not yet resolved, so we decided to demonstrate the effect of catalysts on the stereochemistry of compounds. With the continuation of our previous study, in this, we describe the stereochemistry of DHPM and their stereochemical implications.

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Conflicts of interest: None

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Experimental

Material and Methods

All the chemicals were brought from CDH, Loba Chemie, Merk, and Sigma-Aldrich, and analytical grade solvents were used. All the compounds were prepared with urea, aryl aldehyde, and ethyl acetoacetate in the presence of a brick dust catalyst. To determine the specific rotation, the synthesized compounds were tested digital polarimeter ANTON PAAR of model number MCP 500.

General Procedure

Synthesis of designed derivatives

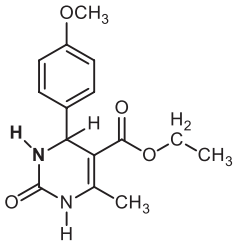
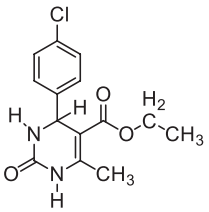
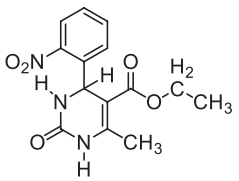
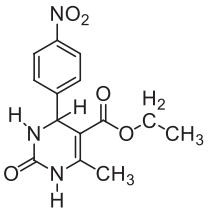
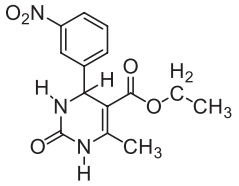
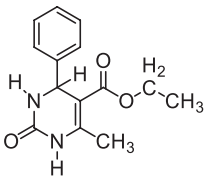
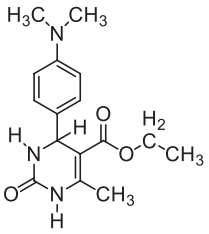
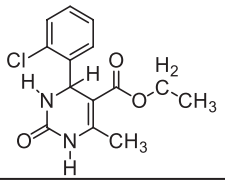
We have synthesized following 12 DHPMs derivatives using brick dust catalyst as per Biginelli reaction.[23,25,27] All the synthesized compounds are given in Table 1.

Procedure for study of stereochemical aspects of synthesized derivatives

Specific rotation of blank solution

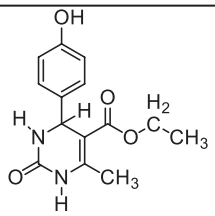
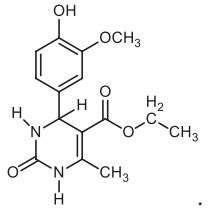
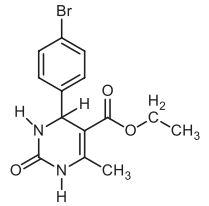
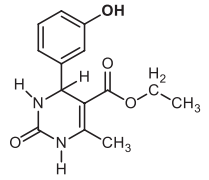
To record the reading of the blank solution, the blank solution (methanol) was placed into a syringe and injected into the cell of polarimeter. Once the machine finished, the complete data

Table 1: Synthesized DHPMs derivatives

S. No.	Code	Structure
1	BD1	
2	BD2	
3	BD3	
4	BD4	
5	BD5	
6	BD6	
7	BD7	
8	BD8	

(Contd...)

Table 1: *(Continued)*

S. No.	Code	Structure
9	BD9	
10	BD10	
11	BD11	
12	BD12	

DPHM: Dihydropyrimidines

including specific rotation and optical rotation were measured at room temperature using a wavelength of 589 nm. To standardize the instrument, the whole procedure was repeated 3 times till the repeatability was achieved.

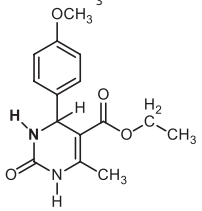
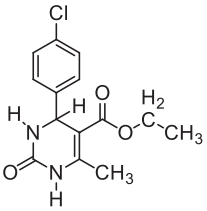
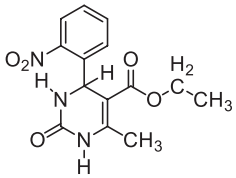
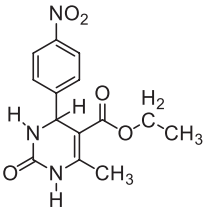
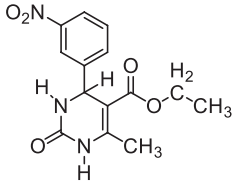
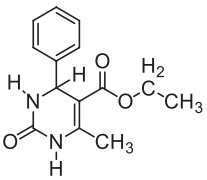
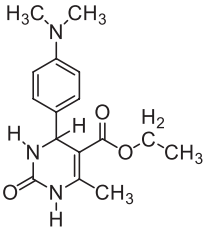
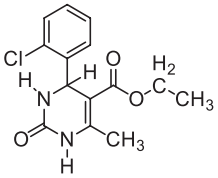
Specific rotation of synthesized derivatives

At room temperature, freshly prepared stock solutions of all the synthesized compounds were prepared. In a beaker, 12 mg of BD-1 was dissolved in 5 ml of solvent (methanol) with continuous stirring until a clear stock solution was obtained. The sample was injected into the pot of a polarimeter at room temperature using a wavelength of 589 nm. The machine begins to record data, with real-time readings at the top-left corner. Once the machine finished, the complete data including specific rotation and optical rotation was measured. Use a syringe filled with a blank solution to clean the polarimeter cell and flush the sample out from the cell. The same procedure was then followed for the rest of the synthesized compounds.

Results and Discussion

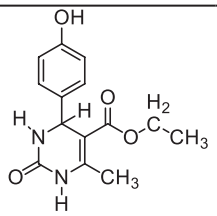
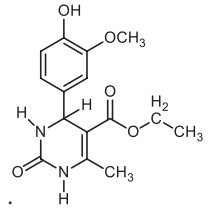
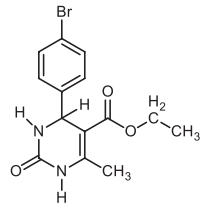
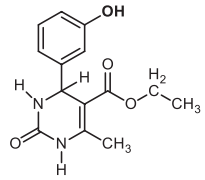
As per Cross and Kelogg, temperature effects the optical rotation and its configuration in various catalytic reactions.[28] In addition, it has also been reported the effect of solvent on the stereochemistry of the compounds by Ko *et al*.[31] It was also studied that, in the presence of non-polar solvents such as acetonitrile, the compounds exhibit strong intramolecular hydrogen bonding between solvent and solutes. However, if the solvent changes

Table 2: Stereochemical data of dihydropyrimidines (DHPMs)

S. No.	*Code*	*Structure*	*Optical rotation*	*Specific rotation*
Blank	Methanol	CH_3OH	−0.003	−1.1
1	BD1		−0.0014	−5.6
2	BD2		−0.021	−8.3
3	BD3		0.003	+1.2
4	BD4		−0.023	−9
5	BD5		0	−0.1
6	BD6		−0.019	−7.4
7	BD7		0.512	+204.8
8	BD8		−0.016	−6.4

(Contd...)

Table 2: *(Continued)*

S. No.	*Code*	*Structure*	*Optical rotation*	*Specific rotation*
9	BD9		−0.026	−10.4
10	BD10		−0.03	−11.8
11	BD11		0	−8
12	BD12		−0.023	−9.2

from acetonitrile to methanol, the repulsion between two dipoles causes conformational changes. Whereas the increase in the concentration of solute also affects the optical activity as the concentration of solute increases, the effect solute-solute interaction decreases the effect of solvent giving the constant value of all the compounds.[29] From the reported data, it is also concluded that the effect of substituent has very less effect on the stereoselectivity of compounds.[30]

All compounds were analyzed at the same temperature, solvent, wavelength, and concentration. As per results of the above data, a variety of aryl aldehydes bearing various types of substituents underwent the reaction to afford the high enantioselectivity [Table 1]. The result indicates that all the dihydropyrimidines have a levorotatory (*S*) configuration except compound BD3 and BD7, which have a dextrorotatory(*R*) configuration, with the electron-withdrawing nitro group at *ortho* position and electro-donating N-dimethyl amino group at the *para* position.

The effect of the catalyst on the stereochemistry of DHPMs was investigated vis the reaction mechanism [Scheme 1]. The increased percentage of SiO_2 on the surface of brick dust was an important factor in the increase in hydroxyl group on the surface of catalyst, which reacted with the carbonyl group of aldehyde and activated it [Step 1, Scheme 1]. In addition, the activated aldehyde further reacted with ethyl acetoacetate and blocked one side of ethyl acetoacetate. The nucleophile (urea) attacks on the opposite side of the molecule, causing SN_2 substitution [Step 2, Scheme 1], resulting in the generation of a chiral center and change in the orientation of the DHPMs as shown in Table 2.

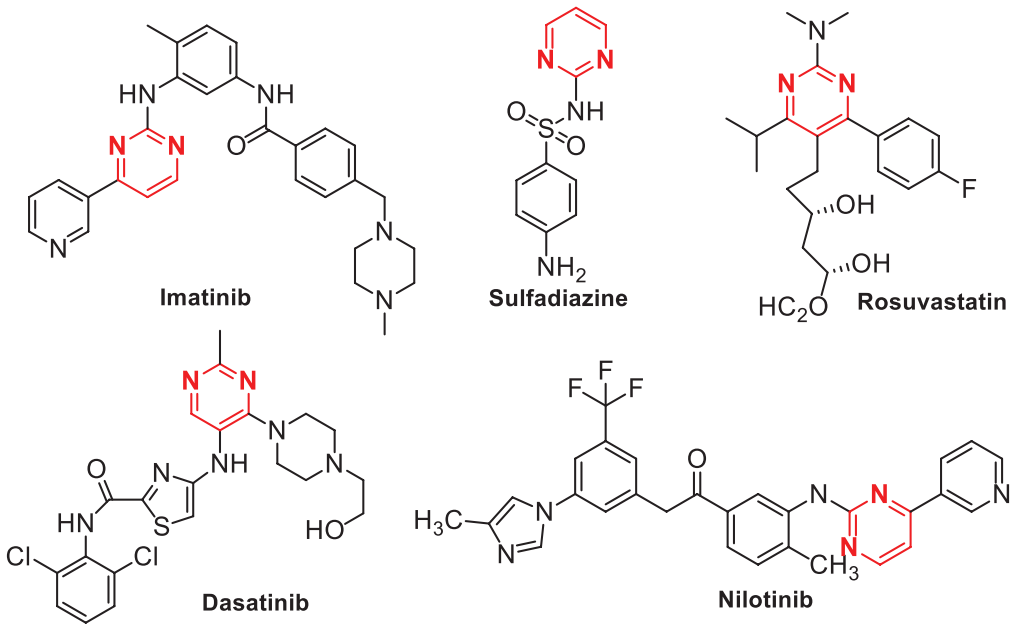
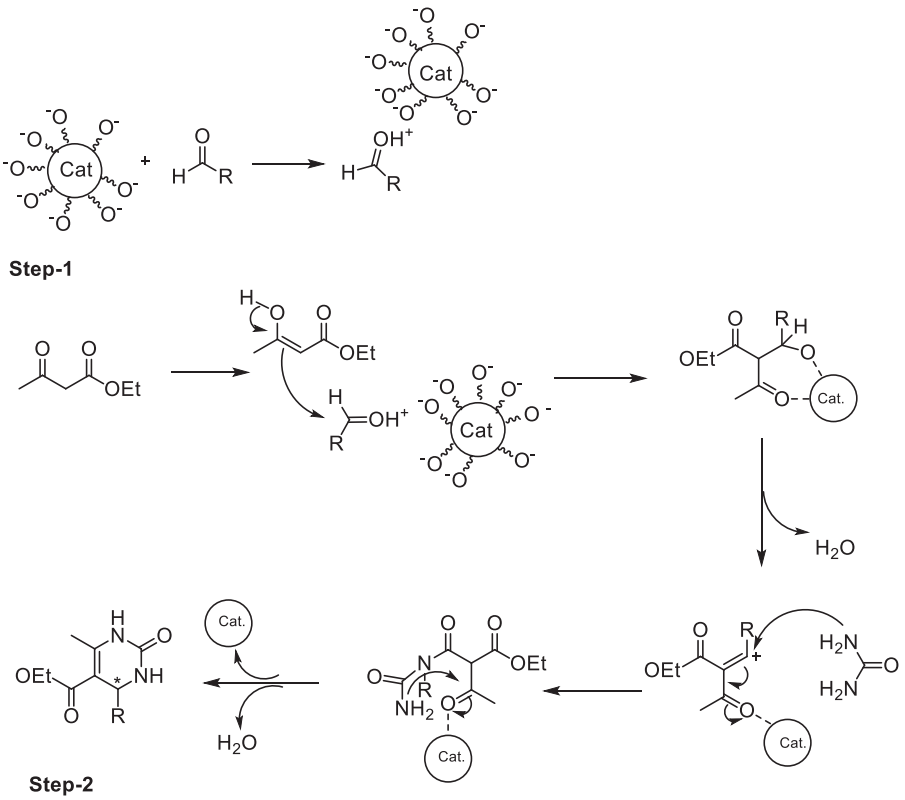


Figure 1: Some of the commercially available pyrimidine derivatives



Scheme 1: Reaction mechanism of DHPMs

Conclusion

DHPMs were prepared using brick dust catalysts in good yield within a short period of time. The influence of the catalyst was studied with its reaction mechanism and it was determined that brick dust catalysts gave the majority of levorotatory products with (*S*) configurations. The main features of this protocol are short reaction time, operational simplicity, high yield, solvent-free, and ease of purification. This new methodology fulfills all the conditions of an efficient reaction and opens the door for the synthesis of a large number of heterocyclic nucleuses.

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