JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

Solvent Less Green Synthesis of Substituted Dihydropyrimidinones and their Sulfur Analogues Using Mild Organic Acids

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Abstract:
One pot three component green synthesis of substituted dihydropyrimidinone and its sulphur Analogues have been reported using mild, simple commercially available organic acids. The reaction was carried out at room temperature without using any solvent by mixing equimolar amount of ethyl acetoacetate, aromatic substituted Benzaldehyde and Urea/Thiourea with catalytic amount of mild acids such as glycine, oxalic acid, maleic acid and vinegar. The kinetics of the reaction was studied by varying the concentration of the acids and substituents on benzaldehyde. It was found that concentration of the acids has significant effect on the kinetics of the reaction. Further there is noticeable effect different acids on duration of product formation mainly attributed to change in pKa of the respective acids. Maleic acid and oxalic acid were found to be excellent catalyst for solvent less synthesis of dihydropyrimidinones and its sulphur analogues using Biginelli reaction with more than 85% yield. Chloro-substituted benzaldehyde moiety gives excellent yield of dihydropyrimidinone with both urea and thiourea. This reaction protocol serves robust and eco-friendly pathway for synthesis of dihydropyrimidinone its sulphur Analogues.

IndexTerms – dihydropyrimidinone, acid catalyst, green synthesis, sustainable

I. INTRODUCTION

Pyrimidine spinoff of heterocyclic compounds such as substituted dihydropyrimidone (DHPM) have attracted masses of scientists working on drugs discovery because of their applications in diverse pharmaceutical utility as drug[1], [2]. These compounds display a huge spectrum of organic activities consisting of anti-inflammatory and antibacterial activity[3].

Pietro Biginelli created the first dihydropyrimidinone molecules. So, the compound is known as Biginelli compound. The reaction involves reflux of aldehydes with urea and a beta ketoester to furnish a tetrahydro pyrimidinone[4]. Conventional synthetic methods have many drawbacks, such as the use of organic solvents, long reaction times, high costs, low yields, unsustainable catalysts, and purification problems[5].

However, for the pharmaceutical and academic sectors, it is necessary to carry out a mild, straightforward, economical, economically advantageous, and environmentally friendly technique for the synthesis of dihydropyrimidinone derivatives with high experimental yield.

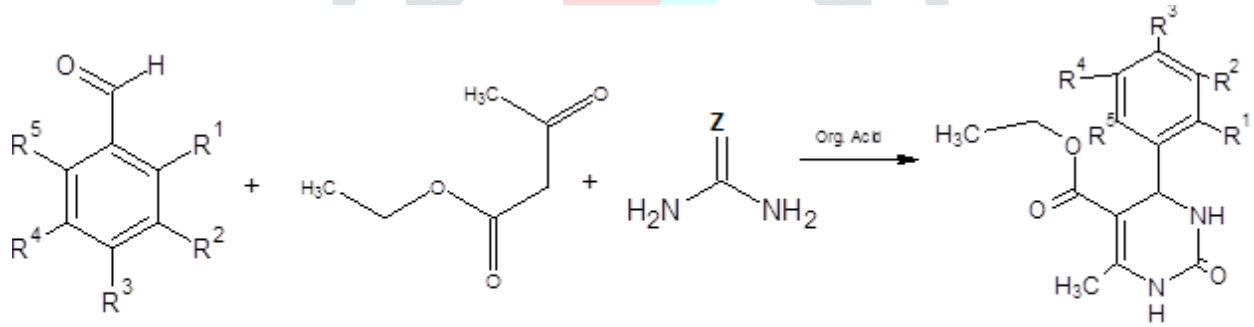
Recently Bahekar et. al. published an article titled “Simple and efficient synthesis of 3,4-dihydropyrimidin-2(1*H*)-thiones utilizing l-proline nitrate as a proficient, recyclable and eco-friendly catalyst”in Journal of Saudi Chemical Society Volume 21, Issue 4, May 2017, Pages 415-419 carried out the synthesis of 3,4 dihydropyrimidin -2(1H)-thiones using L-proline nitrate as a catalyst in modified Biginelli reaction[6].
Gawhale et. al. published an article titled “An expedient synthesis of 3,4-dihydropyrimidin-2(1H) ones derivatives under solvent free condition using titanium dioxide as a catalyst” published in Materials Today: Proceedings Volume

53, Part 1, 2022, Pages 191-195 synthesized Dihydropyrimidones contains pyridine moiety in the ring nucleus using different photocatalysts such as TiO_2, ZnO, ZnS, ZrO_2, StO_2 in solvent free conditions[7].
Though the method disclosed by Bahekar et. al. and Gawhale et. al. is less time consuming, greener and furnish the product in high yield, the catalyst used in the reaction is insoluble in solvent and need to remove or recycle which is tedious and time-consuming job.
Gulati et. al. published an article titled "One-pot three component synthesis of substituted dihydropyrimidinones using fruit juices as biocatalyst and their biological studies" in PLoS ONE 15(9):e0238092 developed a new approach for the synthesis of substituted dihydropyrimidinones derivatives from reaction of equimolar substituted aldehydes, methyl acetoacetate and urea in presence of fruit juices derived from various fruits at room temperature[8]. The method disclosed requires short reaction time mild reaction condition and simple work-up with high yield of product[9].
The method discussed by Gulati et. al directly used fruit juices as an acid catalyst without isolating the individual acid from respective fruit juices which is not advisable in order to understand the kinetics of the reaction. Further it makes the purification of the product difficult.

There is need to perform a very mild, simple, cost-effective, commercially beneficial and eco-friendly procedure for synthesis of dihydropyrimidinone derivatives for the academia and pharmaceutical industries[10].

Committed with this there is great need for improved mild catalyst particularly derived from fruits and vegetable for green chemistry application because they are environmentally friendly, non-hazardous, easily available and inexpensive.

Herein we report one-pot three component green synthesis of subsitituted dihydropyrimidones derivative by using substituted aromatic benzaldehyde, ethylacetoacetate, urea and thiourea at room temperature in presence of mild acid catalyst.



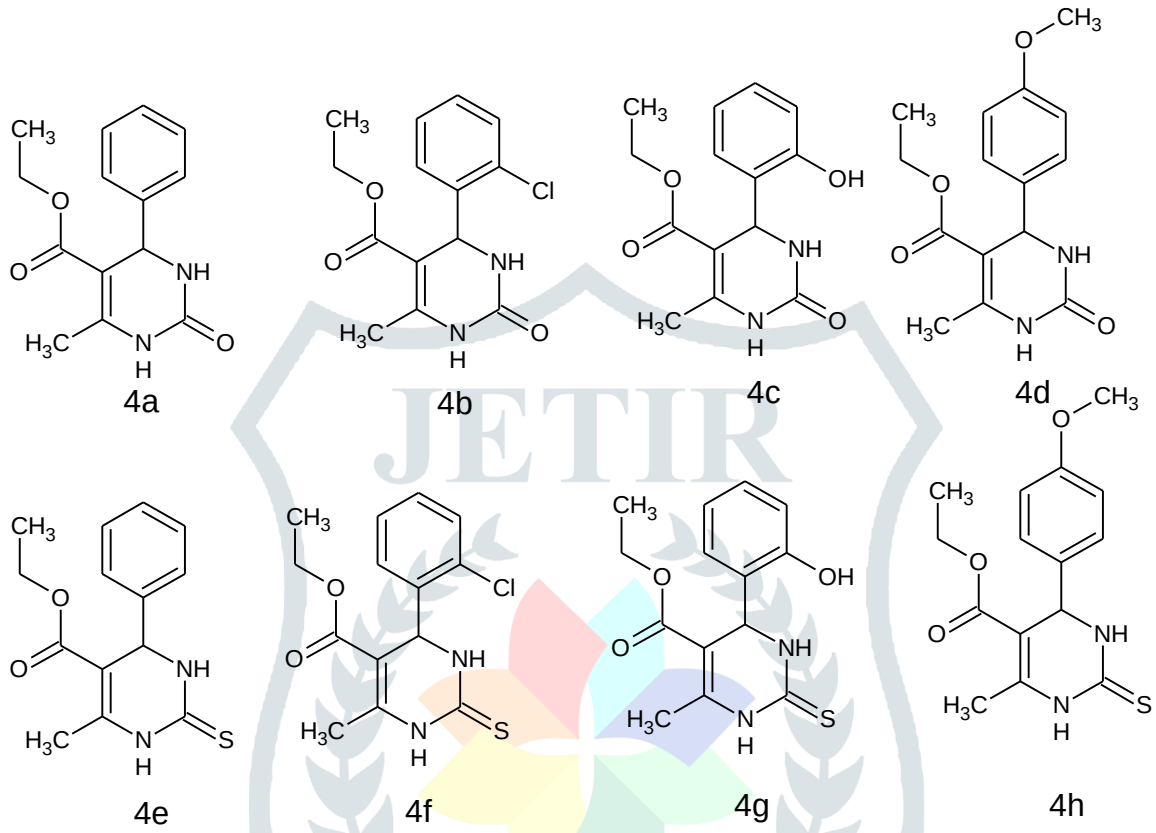
Scheme 1: Green approach to obtain Dihydropyrimidinones and their Sulfur Analogues Using Biginelli Reaction components.

II. EXPERIMENTAL:

2.1 Materials and methods:

All chemicals were purchased from commercial source (Sigma- Aldrich). Reaction were performed in oven-dried glassware washer with chromic acid. The progress of reactions was monitored by thin layer chromatogharphy (TLC) analysis using silica gel as stationary phase on glass slid, solvent combination of mobile phase (Hexane(10): ethyl acetate(90)). Melting point of purified compounds were determined by using Thiels Melting point apparatus. The 1HNMR spectra were recorded in CDCl3 or DMSO-d6 using tetra methyl silane (TMS) as internal reference on "**ECZR Series 600 MHz NMR SPECTROMETER** nuclear magnetic resonance spectrometer. The chemical shifts values are quoted in delta (parts per million, ppm). Infrared spectra (4000-450cm-1) of the synthesized compounds were recorded on **3000 Hyperion Microscope with Vertex 80 FTIR System** and frequency is expressed in cm^{-1}.

2.2 General method: A catalytic amount of mild acid (oxalic acid, malic acid, vinegar, and glycine) was added to the mixture of 1 mole of aromatic aldehyde (o-chlorobenzaldehyde, salisaldehyde), 1 mole of urea, and 1 mole of ethylacetoacetate at room temperature. With the aid of a glass rod, the liquid was physically shaken until the product appeared. For several types of acids, reaction times were observed and yields were calculated. TLC recorded the conclusion of the reaction. Filtering and washing the reaction mixture with the appropriate solvent water were done. By recrystallizing with methanol, the product was cleaned. The IR and NMR measurements of all produced compounds and their melting points were verified.



Scheme 1: Structure of synthesized Dihydropyrimidinones and their Sulfur Analogues Using Biginelli Reaction components.

2.3 Characterization data of selected compounds

1. **4-Phenyl-6-methyl-2-oxo-N-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4a):**
   IR: 3259 cm-1, 3155 (NH), 1674 (C=O of amide).
   1HNMR(300 MHz, DMSO-d6): δ 2.1 (3H, s, CH3-6), 5.4 (1H, s, H-4), 7.1-7.5 (10H, m, Ar-H), 8.1 (1H, s, N1-H), 8.2 (1H, s, NH of amide), 8.9 (1H, s, N3-H).

2. Methyl 6-(2-chlorophenyl)-4-methyl-2-oxo-1,2-dihydropyrimidine-5-carboxylate (4b): 1H NMR (300 MHz, DMSO-d6): δ 2.3 (s, 3H, CH3); 3.4 (s, 3H, COOCH3); 7.2–7.3 (m, J= 8 Hz, 4H, Ar-H); 5.6 (s, 1H, NH); 9.2 (s, 1H, NH)
3. Methyl 4-(2-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4c): 1H NMR (300 MHz, DMSO-d6):δ 1.7 (s, 3H, CH3); 3.7 (s, 3H, COOCH3); 4.5 (s, 1H, OH); 6.7–7.1 (m,J= 8 Hz, 4H, Ar-H); 7.4 (s, 1H, NH); 7.6 (s, 1H, NH)
4. Methyl 6-(4-methoxyphenyl)-4-methyl-2-oxo-1, 2-dihydropyrimidine-5-carboxylate (4d): 1H NMR (300 MHz, DMSO-d6): δ 2.2 (s, 3H, CH3); 3.7 (s, 3H, Ar-OCH3); 3.5 (s, 3H, COOCH3); 6.5–7.6 (m,J= 8 Hz, 4H, Ar-H); 5.1 (s, 1H, NH); 9.1 (s, 1H, NH)
5. **4-Phenyl-6-methyl-2-thioxo-N-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (f):**
   IR in cm-1 : 3384, 3282 (NH), 1672 (C=O of amide), 1438 (C=S).
   H1-NMR (300 MHz, DMSO-d6): δ 2.1 (3H, s, CH3-6), 5.4 (1H, s, CH-4), 7.1-7.9 (10H, m, Ar-H), 9.1 (1H, s, N3-H), 9.3 (1H, s, N1-H), 9.8 (1H, s, NH of amide).

6. **4-(4'-Methoxyphenyl)-6-methyl-2-thioxo-N-phenyl-1,2,3,4- tetrahydro-pyrimidine-5-carboxamide (4h):**

IR cm-1: 3384, 3282 (NH), 1672 (C=O of amide), 1438 (C=S).

1H-NMR (300 MHz, CDCl3/DMSO-d6): δ 2.1 (3H, s, CH3-6), 3.8 (3H, s, OCH3), 5.6 (1H, s, CH-4), 6.7-7.9 (9H, m, Ar-H), 9.4 (1H, s, N1-H), 9.5 (1H, s, N3-H), 10.1 (1H, s, NH of amide).

III. RESULTS AND DISCUSSION

We report the synthesis of 3-4 dihydropyrimidones and their Sulphur derivatives by one-pot three component reaction between equimolar amount of substituted of benzaldehyde ,ethylacetoacete and urea or thiourea in presence of mild acid catalyst at room temperature. Above physical data of this study are presented in after completion of the reactions. The solid product was collected by simple filtration without further purification.

The reaction conditions were optimized by varying the concentrations of substituted benzaldehyde, ethyl acetoacetate, urea and thiourea in the presence of mild acid catalysts such as maleic acid, vinegar, glycine, and oxalic acid. The desired product is obtained within 20 to 25 minutes and yields up to 89%.

The kinetics of the reaction was studied w.r.t. type of acid catalyst, concentration of the acid catalyst, and substituent on benzaldehyde moiety. It was found that the duration of the reaction varies with the type of acid, as shown in Table 1. The reaction with Urea completes within 25 minutes for malic acid and oxalic acid; however, it takes about 1 hour for vinegar and glycine as an acid catalyst. The same reaction with its sulfur analogues is very slow for all the acid catalysts. This decrease in rate of reaction with different acids is due to a change in the pKa value of the reaction[11]. Oxalic acid and Maliec with the least pKa value show a faster reaction. However, it was observed that there is no noticeable effect on the yield of the reaction.

Entry	Acid Catalyst/pKa	Urea		Thiourea	
		Time(Min)	Yield(%)	Time(Min)	Yield(%)
1	Maliec acid (1.83)	25	88	160	85
2	Oxalic acid(1.2/4.2)	25	87	160	87
3	Vinegar (4.76)	60	87	380	86
4	Glycine(2.35)	60	89	380	86

Table 1: Model reaction to study kinetics of reaction w.r.t. type of acid using anisaldehyde, ethyl acetoacetate and urea or thiourea

Further the kinetics of the reaction was studied with concentration of the acid catalyst. It was observed that there is remarkable effect of the concentration of acid catalyst on duration of reaction as more reactant molecules get activated due to more amount of acid which triggers the condensation process rapidly[12]. Further there is little or no change in the yield of the DHPM products as shown **Table 2.** Similar results were obtained for thiourea analogues.

Entry No.	Concentration of Oxalic acid (nM)	Urea		Thiourea	
		Time(Min)	Yield(%)	Time(Min)	Yield(%)
1	25	25	88	120	89
2	50	20	89	100	87
3	100	8	87	120	88
4	150	5	85	121	88

Table - 2: Model reaction to study kinetics of reaction w.r.t concentration of acid using Oxalic acid with anisaldehyde, ethyl acetoacetate and urea or thiourea

Various derivatives of DHPM and its sulfur analogues were obtained using substituted benzaldehyde. The effect of the substituent on the duration of the reaction and yield of the product was also studied. It has been observed that there is no significant effect on the duration of reaction or yield of reaction for selected substituents in benzaldehyde as shown **Table 3**.

Entry No.	Substituent on Aromatic aldehyde	Urea		Thiourea	
		Time(Min)	Yield(%)	Time(Min)	Yield(%)
1	H	22	88	120	89
2	2-Cl	20	89	100	87
3	2-OH	21	87	120	88
4	4-OMe	21	85	121	88

Table 3: Effect of substituents on the aromatic aldehyde rate of reaction studied using Oxalic acid as acid catalyst, ethyl acetoacetate with urea or thiourea

IV. CONCLUSION

In conclusion , the present work provides facile synthesis of substituted dihydropyrimidinones and its sulphur analogue by one-pot three component condensation of substituted benzaldehyde, ethyl acetoacetate and urea or thiourea at room temperature in presence of mild acids in excellent yield. The study further provides the optimized conditions to obtain high yield of the product with less time. The current method has numerous benefits, including an easy-to-use catalytic system, no use of hazardous chemicals, eco-friendly solvents, a quick reaction time, and high yiel

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