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Multicomponent Biginelli Synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones by grindstone technique and evaluation of their biological properties.

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ABSTRACT

The purpose of this study was to synthesize substituted 3,4-dihydropyrimidin-2(1H)-ones (DHP) and to evaluate them for their antibacterial and antifungal activities. These compounds were synthesized by cyclocondensation reaction between 3,4-dimethoxybenzaldehyde (veratraldehyde), active methylene compounds (acetyl acetone or acetoacetic ester) and urea / thiourea in presence of $CuCl_2.2H_2O$ and HCl by grindstone technique. The products are obtained in good yield under mild, solvent free and ecofriendly conditions. The structures of these compounds have been confirmed on the basis of their IR and NMR spectral data. The dihydropyrimidinone derivatives synthesized have been tested for antibacterial activity against Micrococcus luteus, Escherichia coli & Pseudomonas aeruginosa and for antifungal activity against Aspergillus niger, Candida albicans & Candida kefyr.

Keywords: 3,4-dihydropyrimidin-2(1*H*)-ones, Biginelli reaction, grindstone chemistry and antimicrobial activity

INTRODUCTION

In organic and medicinal chemistry multicomponent reactions are gaining importance for various reasons. Synthesis of dihydropyrimidinones (DHP) by Biginelli reaction is one among them. Biginelli reaction is an acid catalyzed cyclocondensation reaction of a β-ketoester with an aldehyde and urea to yield DHP.The pyrimidine skeleton is available in a wide variety of naturally occurring compounds and also in clinically useful molecules having diverse biological activities and hence, it is of great importance to chemists and biologists [1-11]. Dihydropyrimidinones have

attracted considerable interest because of their pharmacological and therapeutic properties [12-18]. They exhibit interesting biological effects such as antiproliferative [19], antiviral [20], anti-tumour [21], anti-inflammatory [22], antibacterial [23], antifungal [24], antitubercular [25], anti-histaminic [26] and anti-analgesic [27] activities. Biginelli condensation is an important 'Multi-component Reaction' for the construction of DHP. Traditional Biginelli reactions were conducted under strongly acidic conditions which suffer from poor yields and long reaction duration. The synthesis of these compounds has gained importance and plethora of improved synthetic methodologies has been recently reported. Most commonly PPE [28], lanthanide compounds [29-30] and various Lewis acids [31-32] were used as promoters. Recently NH_4Cl [33], ionic liquids [34], heteropolyacids [35], montmorrillonite -KSF [36], ultrasonic[37] and microwave irradiation [38] have also been used for Biginelli reaction. Although many Lewis acids and transition metal salts have been found to catalyze this reaction, they still have limitations like high cost, limited availability, prolonged reaction duration and the use of strong acids. Therefore, search for a milder and more efficient protocol for the synthesis of dihydropyrimidinone continues to draw the attention of researchers.

The advantages of the grindstone technique include high yields, environmentally benign procedure, shorter reaction time, simpler workup procedure and less energy consumption. Solvent free condition is especially suitable for providing an eco-friendly system and it avoids problems associated with the use of organic solvents such as cost, handling, safety and pollution. The solvent free reaction condition is an important object of green chemistry. To overcome the barriers associated with solvent free reactions, the mechanochemical mixing *i.e.*, grinding is adopted. Herein, $CuCl_2.2H_2O$ as an efficient catalyst [39] has been reported for the synthesis of DPH at room temperature solvent free conditions with enhanced reaction rates & high yields (scheme-1).

EXPERIMENTAL SECTION

All chemicals used were of AR grade. The reactions were monitored by TLC using silica gel 60-120 mesh. Melting points were recorded by open capillary method and are uncorrected. IR spectra were recorded on Perkin -Elmer FTIR-240C spectrophotometer on KBr disc. ^{1}H- NMR spectra were recorded on 300 MHz spectrometer in $CDCl_3$ using TMS as internal standard.

General Procedure for Synthesis of dihydropyrimidinones

A mixture of a substituted aromatic aldehyde *i*.e., veratraldehyde (10 mmol), ethyl acetoacetate / acetyl acetone (10 mmol), urea / thiourea (20 mmol) , $CuCl_2.2H_2O$ (5 mmol) and a few drops of con.HCl was ground together for 2-5 minutes using a mortar and pestle of appropriate size. The initial syrupy reaction mixture solidifies within 5-20 minutes. The solid mass was left overnight, then washed with cold water and purified by recrystallization from ethanol to afford the desired dihydropyrimidinones (IA-IIB).The obtained products were characterized by means of spectral (IR & 1H-NMR) data and their melting points.

Antimicrobial activity

In this work, we report the *in vitro* study of antimicrobial activity of dihydropyrimidinones against Gram +ve bacterium (Micrococcus luteus,) , Gram –ve bacteria (Escherichia coli & Pseudomonas aeruginosa) and fungi (Aspergillus niger, Candida albicans & Candida kefyr).

Antimicrobial assay

Antibacterial analysis was followed using standard agar well diffusion method [40-42] to study the antimicrobial activity of the compounds Each bacterial and fungal isolate was suspended in Brain Heart infusion (BHI) broth and diluted to approximately 10^5colony forming unit (CFU) per mL. They were flood-inoculated onto the surface of BHI agar and then dried. Five-millimeter diameter wells were cut from the agar using a sterile cork-borer and 30 µL (5µg compound in 500 uL DMSO) of the sample solution were poured into the wells. The plates were incubated for 18 h at 37^{o}C for bacteria and at room temperature for fungi. Antimicrobial activity was evaluated by measuring the zone of inhibition in mm against the test microorganisms. DMSO was used as solvent control. Ciprofloxacin was used as reference antibacterial agent and ketoconazole was used as reference antifungal agent. The tests were carried out in triplicates. The results of *in vitro* study of antimicrobial activity of DHP against each of the three bacterial species (Micrococcus luteus, Escherichia coli, Pseudomonas aeruginosa) and three fungal species (Aspergillus niger, Candida albicans, Candida kefyr) are reported the tables II & III.

BRAIN HEART INFUSION (BHI) AGAR

Composition

Calf brains (infusion from 200g) 12.5
Beef heart (infusion from 250g) 5.0
Proteose peptone 10.0
Sodium chloride 5.0
D(+)-Glucose 2.0
Disodium hydrogen phosphate 2.5
Agar 10.0
Final pH 7.4 + /- 0.2 at 37^o C

Store prepared media below 8^o C, protected from direct light. Store dehydrated powder, in a dry place, in tightly –sealed containers at 2-25^o C.

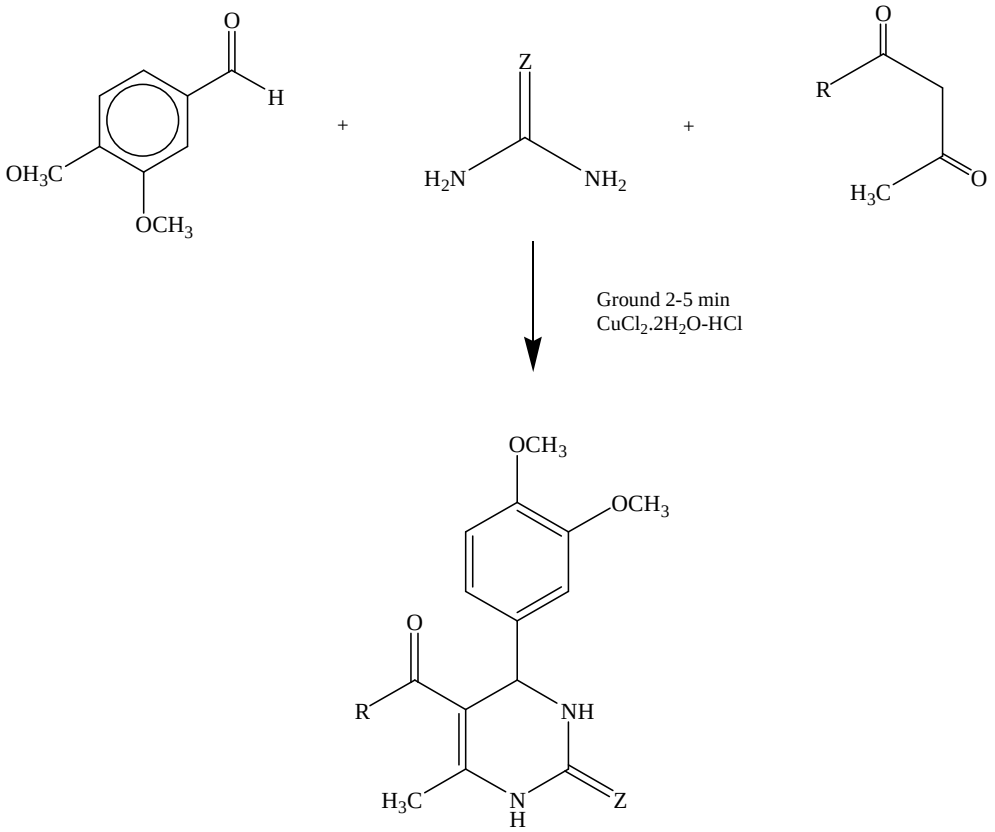
Directions:

The above ingredients were suspended in 1 liter of distilled water, boiled to dissolve the medium completely distributed into tubes, plates or flasks and sterilized by autoclaving at 121^o C for 15 minutes.

The cytotoxicity of DHP was compared with ciprofloxacin for antibacterial study and ketoconazole for antifungal study. The zone of inhibition was expressed in mm and compared with standard drugs used.

RESULTS AND DISCUSSION

Scheme-1



Where, R = C_2H_5O or CH_3 and Z = O or S

Table-I : Physical characterization data of compounds

Entry	R	Z	M. P. (^{O}C)	Yield(%)
IA	CH_3	O	186-188	88
IB	CH_3	S	114 – 116	87
IIA	C_2H_5O	O	176 – 177	92
IIB	C_2H_5O	S	172 – 174	94

Spectroscopic data:

5-Acetyl-4-(3,4-dimethoxyphenyl)-6-methyl-3,4-dihydropyrimidine-2-one (IA)

IR (KBr,cm^{-1}): 3300 (N-H), 2933 (C-H) , 1698 (C=O) , 1513 (C=N) , 1420 (Ar C=C) , 1234 (C-O)

1H NMR ($CDCl_3$) : 2.14 (s , 3H , CH_3) , 2.372 (s, 3H, $COCH_3$) , 3.873 (S, 6H, OCH_3) , 5.455 (d, 1H, CH) , 5.989 (s,1H, NH) , 6.832 (m, 2H, ArH) , 7.287 (s,1H, ArH) , 8.153 (s,1H, NH)

5-Acetyl-4-(3,4-dimethoxyphenyl)-6-methyl-3,4-dihydropyrimidine-2-thione (IB)

IR (KBr, cm^{-1}): 3382 (N-H), 3171, 2967 (C-H) , 1674 (C=O) , 1511 (C=N) , 1460 (Ar C=C) , 1393 (C-O)

1H NMR ($CDCl_3$) : 2.14 (s ,3H ,CH_3) , 2.372 (s, 3H, $COCH_3$) , 3.873 (s, 6H, OCH_3) , 5.455 (d, 1H,CH) , 5.989 (s,1H, NH) , 6.832 (m, 2H, ArH) , 7.287 (s,1H, ArH) , 8.153 (s,1H, NH)

Ethyl-4-(3,4-dimethoxyphenyl)-6-methyl-2-oxo-3,4-dihydropyrimidine-5-carboxylate (IIA)
IR (KBr, cm^{-1}): 3283 (N-H), 3179, 2976 (C-H), 1701 (C=O), 1513 (C=N), 1463 (Ar C=C) ,1392, 1260 (C-O)
1H NMR ($CDCl_3$) : 1.2 (t ,3H ,CH_3 of CH_3CH_2O) , 2.345 (s, 3H, $COCH_3$) , 3.8(s, 6H, OCH_3) , 4.1 (q, 2H, CH_2 of CH_3CH_2O), 5.39 (d,1H, CH_2), 6.8 (m, 2H, ArH), 7.3 (s,1H, ArH), 8.24 (s,1H, NH)

Ethyl-4-(3,4-dimethoxyphenyl)-6-methyl-2-thioxo-3,4-dihydropyrimidine-5-carboxylate (IIB)
IR (KBr, cm^{-1}): 3250 (N-H), 2931 (C-H), 1717 (C=O), 1517 (C=N), 1459 (Ar C=C), 1377 (C=S), 1286 (C-O)
1H NMR ($CDCl_3$) : 1.2 (t ,3H ,CH_3 of CH_3CH_2O),2.35 (s, 3H, $COCH_3$), 3.86 (S, 6H, OCH_3), 4.1 (q, 2H, CH_2 of CH_3CH_2O), 5.38 (d, 1H, CH), 6.03 (s,1H, NH), 6.8 (m, 2H, ArH), 7.3 (s, 1H, ArH), 8.46 (s, 1H, NH)

Table-II

S. No.	Organisms (Bacteria)	Zone of Inhibition (mm)				Ciprofloxacin
		IA	IIA	IB	IIB	
1.	*Micrococcus luteus*	17	20	21	14	20
2.	*Escherichia coli*	20	13	18	14	19
3.	*Pseudomonas aeruginosa*	10	7	10	8	15

Table-III

S. No.	Organisms (Fungi)	Zone of Inhibition (mm)				Ketoconazole
		IA	IIA	IB	IIB	
1.	*Aspergillus niger*	-	I2	18	5	15
2.	*Candida albicans*	25	20	22	-	19
3.	*Candida kefyr*	25	25	34	-	16

The DHP IIB showed poor activity against both the bacterial species and fungicidal species. IA exhibited moderate activity against bacterial species. IIA and IIB showed good activity against bacterial species. It is noteworthy that all the three compounds IA, IIA and IIB have shown promising activity against the fungal species as comparable to the standard drug ketoconazole.

Antimicrobial activity
It is interesting to note that DHP synthesized from 4-methoxybenzaldehyde using the same procedure by our research team showed no activity against the same bacteria and fungi. However, DHP reported in this work prepared using 3,4-dimethoxybenzaldehyde (veratraldehyde) showed mild to very good activity against bacteria and fungi.

CONCLUSION

In summary, we have developed a simple, efficient and more eco-friendly grinding technique for the synthesis of 3,4-dihydropyrimidinone using veratraldehyde. The notable advantages of this method include no usage of solvent (except for recrystallization), simple reaction profile, shorter reaction time (4-5mins) and high yields (87-94%).

The antimicrobial searching suggests that all the newly synthesized Biginelli compounds showed moderate to very good activity against the tested organisms. Among the compounds, IB showed the most promising antibacterial and antifungal activity, suggesting further work with similar analogues.

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