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Modified Biginelli Reaction Catalyzed by Cobaltous Chloride Conducted in Microwave

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Abstract— 3, 4- Dihydropyrimidine -2(1H)-Ones were synthesized efficiently using $CoCl_2.6H_2O$ as catalyst. The reaction was conducted by microwave irradiation without using any solvent. The prevased derivatives are expected antiviral, antitumor, antibacterial and anti-inflammatory action and used in treatment of cardiovascular diseases. These are remarkable pharmacological efficiency and calcium channel blockers.

Keywords— *Microwave, $CoCl_2$ $6H_2O$, Mlticomponent reaction, Biginelli Reaction, Calcium channel blockers, dihydropyrimidinone*

INTRODUCTION

Polyfunctionalized heterocyclic compounds play important roles in the drug discovery process and analysis of drugs in late development the market shows that 68% of them heterocycles[1,2]. The pyrimidine heterocyclic core is an important subunit because of its wide spread abundance in the basic structure of numerous natural products [3, 4]. In 1893 the Italian Chemist Pietro Biginelli reported a cyclocondensation reaction between ethyl acetoacetate , benzaldehyde and urea to obtain a heterocyclic system of dihydropyromidinone (DHPM) (Scheme-1), which is known as Biginelli reaction[5,6]. Due to increasing concern about the environment, there has been great interest in the development of organic chemical processes that use more environmental freindly being alternatives in terms of product selectively, operational simplicity and environmental safety [7].Multi component reaction (MCRs) have recently gained tremendous important in organic & medicinal chemistry. The main contributing factors are the high atom economy wide application in combinational chemistry and diversity – oriented synthesis [8, 14]. Dihydropyrimidones are attractive organic compounds which show important biological activities such as antiviral , antitumor , antibacterial & anti-inflammatory action [15].

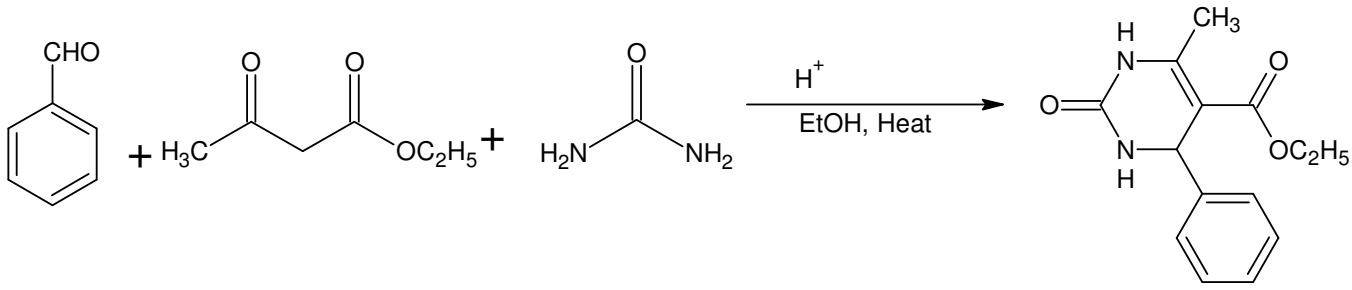
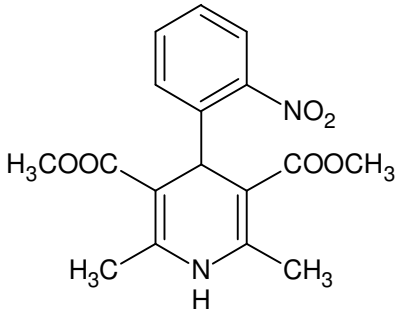


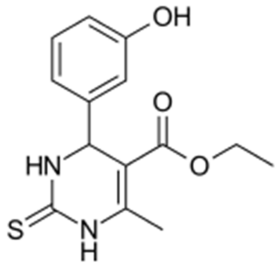
Figure: 1

Scheme 1: The Biginelli dihydropyrimidinone synthesis.

4-Aryl-1,4-dihydropyrimidines of the nifedine type (eg:1) were first introduced in to chemical medicine[16].Dihydropyrimidines type show a very similar pharmacological profile, and in recent years, several related compounds were developed (eg:2)that are equal in potency and duration of antihypertensive activity to classical and second – generation dihydropyrimidine drugs[17].



Nifedipine (1)



(2)

Figure: 2

These are compounds were first introduced into clinical medecine in 1975 [19]. These are remarkable pharmacological efficiency and calcium channel blockers [18]. Even today these medicines are used for the treatment of cardiovascular diseases [20]. The part of performing efficient chemical transformation coupling three component in a single operation by a catalytic process avoiding stoichiometric toxic reagents, large amounts of solvents, and expensive purification techniques represents a fundamental target of the modern organic synthesis [21,22]. Thus , Biginelli' s reaction for the synthesis of dihydropyrimidinones has received renewed interest , and several improved procedures have recently been reported, consequently , there is scope for further renovation towards mild reaction conditions , increased variation of the substituent's in all three components, and better yields under microwave irradiation[23-28]. Several alkaloids containing the dihydropyrimidine core unit have been isolated from marine sources,which also exhibit interesting biological properties. Most notably, These compounds inhibit the binding of HIV envelope protein gp-120 to human CD4 cell and therefore , are potential new leads for AIDS therapy . Recently, DHPMs are also shown to be useful for the development of anticancer drugs [29, 30].

RESULTS AND DISCUSSION

Results on the Biginelli reaction over different supported and unsupported metal chloride catalysts under the microwave irradiation for a total period of 3.0 min. to 6.0 min. are presented in table 1,

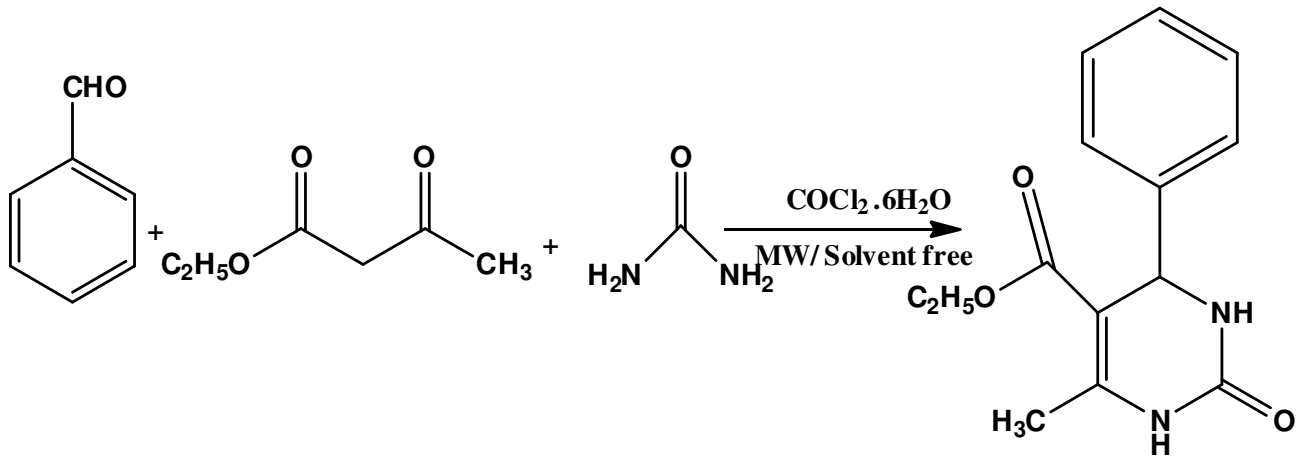
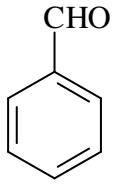
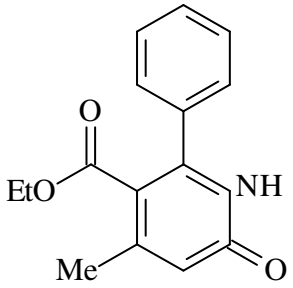
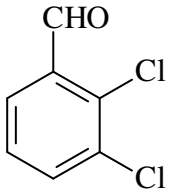
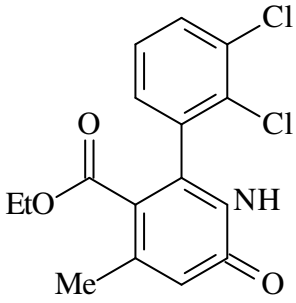
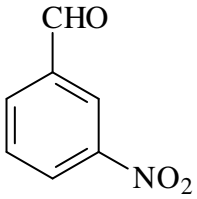
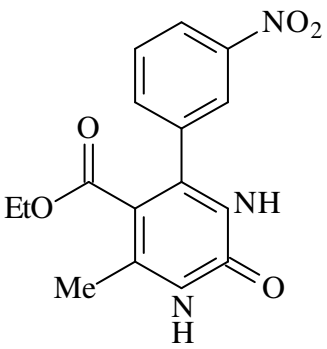
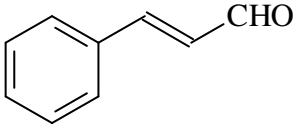
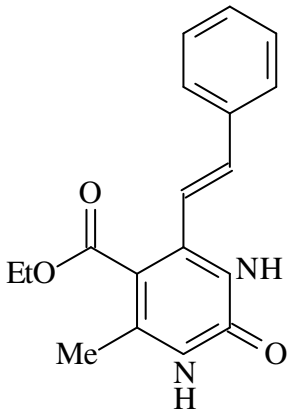
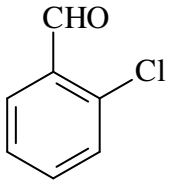
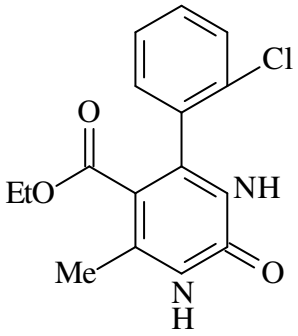
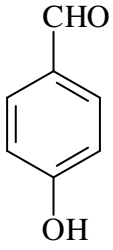
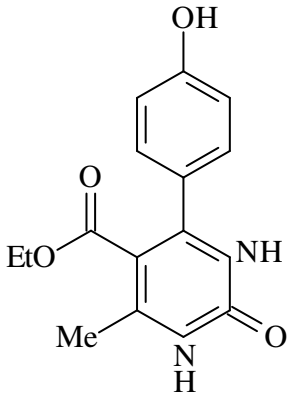
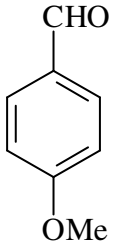
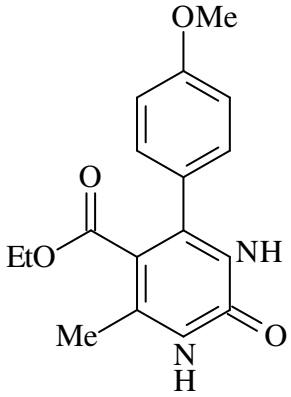
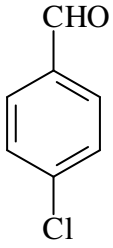
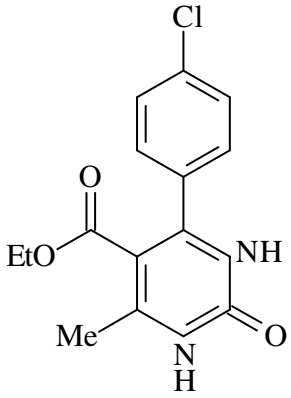


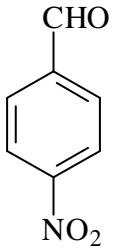
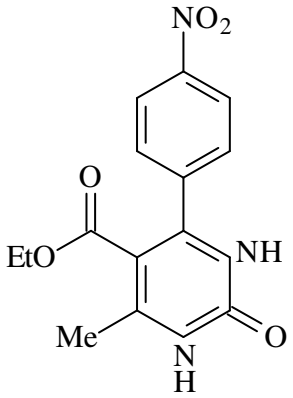
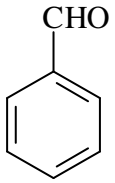
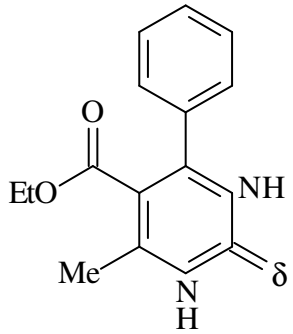
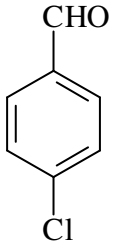
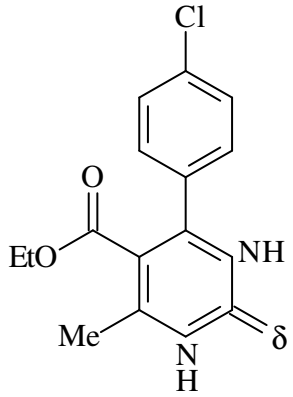
Figure:3

Scheme – 2
(whereZ= p-nitrp, p-chloro, 2,4-dichloro,3-nitro,2-nitro,p-OH,4-OCH_4,etc.)

Table 1: Catalyst $CoCl_2\,6H_2O$ – Catalyzed synthesis of dihydropyrimidinones / thiones.

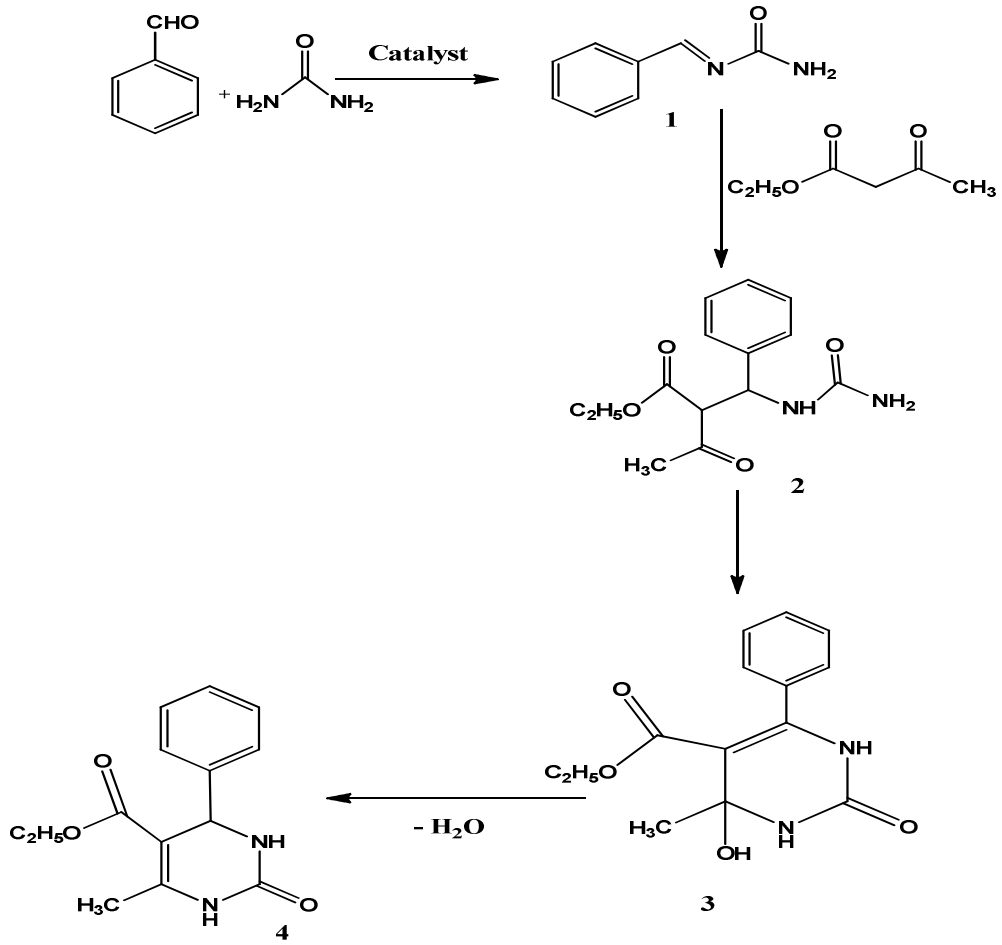
Entry	Substrate	Rx product	M.W. irradiant	Yield	M.P.
1			3.5 min	85%	202
2			4.0min	79.7%	209
3			3.5min	76.5%	206
4			4.5min	77.9%	212

5			4.omin	65.7%	210
6			3.omin	64%	205
7			3.5min	78.825%	210
8			5.0min	76%	212

9			4.0min	69.9%	205
10			3.omin	70%	205
11			5.0min	68%	211

It is interesting to note that, even in the obsence of catalyst the reaction accurs but with a much lower product yield (20%). The product yield is increased in the presence of the homogeneous metal chloride (ie. $ZnCl_2$, $AlCl_3$, &$FeCl_3$) catalysts. The metal chloride like Cobaltous Chloride ($CoCl_2$ $6H_2O$) shows a better performance in the Biginelli reaction. The increased activity in the present case may be due to formation of more active sites as a result of interaction of metal chloride with support. A further work is necessary for understanding the support effect.

Results of the Biginelli reaction with different aromatic aldehyde substrates using the best- selected catalyst .$CoCl_2$ $6H_2O$ are presented in table 1. Biginelli reaction with different substituted benzaldehydes or other aromatic aldehydes for the synthesis of corresponding DHPHs with high yield without using any solvent in microwave for a very short reaction period up to 6.0 min. and easy workup (Scheme-2). In summery a new and efficient modified Biginelli reaction has been described, The advantages of this environmently benign reaction including the simple reaction set-up high product yield. The mechanism of a three components reaction has been studied in the present study (Scheme-3)



Scheme 3: A plausible mechanistic pathway using aldehyde ,ethylacetoacetate and urea.

GENERAL PROCEDURE

The Biginelli reaction was carried out by a mixture of aldehyde 1(mmol), ethylacetoacetate 1(mmol), urea/ thio urea 3(mmol) and catalyst $CoCl_2$ $6H_2O$ 1(mg) without any solvent in a 50 ml glass flask . After the mixture was stirred for 40 sec with a spatula, the reaction container was irradiated in MW oven 4 time at 40% power of total 700W for 30s. with 1 min. cooling period after each irradiation. The reaction was monitored by TLC. The total period of the MW irradiation was 3.0 to 6.0 min. After the reaction ,the reaction mixture was cooled at room temperature and poured into ice .The resulting product was washed with water and dried . The solid was re-crystallized by a small amount of ethanol to yield the product.

Conclusions: $CoCl_2$ 6H O is a highy environ – friendly catalyst for one-pot synthesis of large size dihydropyrimidinone molecules by Biginelli reaction without using any solvent.

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