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Ni $(ClO_4)_2.6H_2O$ an Efficient Catalyst for One-Pot Synthesis of Dihydropyrimidinones

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Abstract: **3,4-dihydropyrimidin-2-(1*H*)-ones were synthesized in high yields through Biginelli condensation reactions of aldehydes, 1,3-dicarbonyl compounds and urea or thiourea using Nickel (II) perchlorate as a catalyst under solvent-free conditions. Readily available reagent, inexpensive and eco-friendly catalyst. This method provides the modified synthesis of biologically active compounds such as much Nifedipine and Amlodipine, in terms of high yield, short reaction time and simple workup procedure.**

***Keywords*: Nickel perchlorate; Biginelli reaction; solvent-free; dihydropyrimidinones; one-pot condensation.**

1. INTRODUCTION

The original Biginelli dihydropyrimidine condensation (1893) reaction possesses the early example of the cyclocondensation process which was involving an aromatic aldehyde, β- ketoester and urea. The scope of the heterocycle synthesis has been extended now considered by the variation of all three building blocks. While using this method, several numbers of multifunctionalized pyrimidine derivatives were synthesized.

There are several reports are available for therapeutic and pharmaceutical properties of Dihydropyrimidinones and their derivatives such as antiviral, antibacterial, anti-inflammatory and antitumor activities[1-3]. The recent report was mentioned that functionalized dihydropyrimidinones have been successfully used as adrenergic, neuropeptide Y (NPY) calcium channel blockers, antagonists and antihypertensive agents[4,5]. In addition, some of the marine sources have alkaloids containing the dihydropyrimidine core unit and also shows the interesting biological properties especially HIV gp-120-CD4 inhibitors[6,7].

Today at least a hundred different experimental reaction conditions are known for Biginelli condensation. For the condensation of Benzaldehyde with ethyl acetoacetate and urea. Traditionally, Biginelli condensations are carried out in a variety of solvents such as ethanol or methanol, but more recently aprotic solvents such as THF, dioxane or acetonitrile have also been used successfully. In some cases, it is necessary to use acetic acid as a solvent [8] Recently, many synthetic methods for preparing these compounds have been developed to improve and modify this reaction by using Lewis acid catalysts as well as protic acids including $FeCl_3{\cdot}6H_2O$, $NiCl_2{\cdot}6H_2O$ [9], lanthanide triflate [10], H_3BO_3 [11], VCl_3 [12], $Sr(OTf)_2$ [13], PPh_3 [14], Indium(III) halides [15], LiBr [16], Silica sulfuric acid [17], $Mn(OAc)_3{\cdot}2H_2O$ [18], $Y(NO_3)_3{\cdot}6H_2O$ [19], $In(OTf)_3$ [20], $TaBr_5$ [21], $Ce(NO_3)_3{\cdot}6H_2O$ [22], silica chloride [23], HCOOH [24], $SrCl_2{\cdot}6H_2O$-HCl [25], $Yb(OTf)_3$ [26], $Bi(NO_3)_3{\cdot}5H_2O$ [27], tungstate sulfuric acid [28], $HClO_4$- SiO_2 [29] and so on. In addition, microwave irradiation [30] ultrasound irradiation [31] and ionic liquids [32-41], were also utilized as the catalytic condition. However, in spite of their potential utility, many of these methods involve expensive reagents, strong acidic conditions and long reaction times.

Perchlorates are of great chemical interest and importance, on the other hand, because they possess several unique properties. They have large degrees of ionic character; the perchlorate ion, in fact, has a very high electronegativity, which corresponds to a high solvation energy. This is a major factor in the high solubilities of most of the perchlorates in water and in a large number of nonaqueous solvents. The most commonly employed perchloric acids are $LiClO_4$, $Mg(ClO_4)_2$, $Zn(ClO_4)_2{\cdot}6H_2O$, and $Ni(ClO_4)_2{\cdot}\ 6H_2O$ [42] act as powerful Lewis acids, with this character mainly being exploited to activate bidentate compounds. Many of the metal perchlorates to have found application in organic chemistry,

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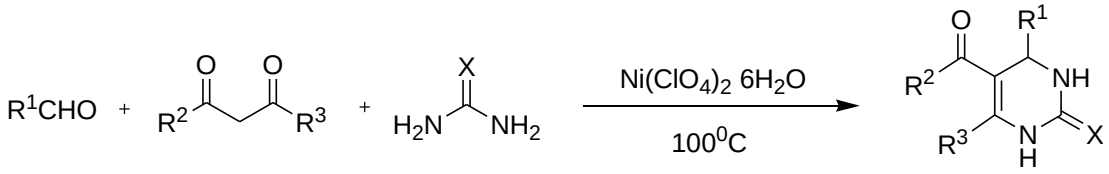
Here we wish to the results obtained from a study of the preparation 3,4-dihydropyrimidin-2-(1*H*)-ones with $Ni(ClO_4)_2 \cdot 6H_2O$ as an inexpensive and easily available catalyst under neutral and solvent-free conditions (Scheme 1). The procedure gives the products in good yields and avoids problems associated with solvent use (cost, handling, safety, and pollution) [43]. Decreased reaction times are also realized because of the increased reactivity of the reactant in the solid state and the fact that the other reaction product, water, evaporates at the reaction temperature of 100^0C. While using the same methodology we are synthesized two biologically active compounds namely Nifedipine and amlodipine.

We performed reactions using different quantities of reagents and solvents to improve the yields. The best results were obtained with a 10 mol% of Nickel (II) perchlorate, 1 equivalent of aldehyde and 1.5 equivalent of 1,3-dicarbonyl compound and Urea or thiourea.



R^1 = Alkyl and Aryl
R^2 = Alkyl-O and Alkyl
R^3 = Alkyl, Aryl and Methoxy methyl

X = O, S

(**1-26**)

Scheme 1.

Experimental

Nickel (II) perchlorate – catalyzed synthesis of 5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one, under solvent–free conditions

A solution of ethyl acetoacetate (1.5 equiv.), benzaldehyde (1 equiv.) and urea (1.5 equiv.) was heated under 100°C in the presence of Nickel (II) Perchlorate (10 mol%) for 50 min (monitored by TLC, Hexane: Ethyl acetate ratio is 40:60 percentage) under air atmosphere. The reaction mixture after being cooled to room temperature was poured into crushed ice (20 gm) and stirred for 5-10 min. The solid separated was filtered under section (water aspirator), washed with ice-cold water (20 mL) and then recrystallized from hot ethanol to afford the pure product with good yield. This procedure was followed for the preparation of all the dihydropyrimidinones and thiones listed in Table 1. The known compounds have been identified by comparison of spectral data (IR, ^{1}H NMR, and ^{13}C NMR) with those reported.

Table 1: Nickel (II) perchlorate synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones under solvent-free conditions at 100^0C

DHMP[a]	R^1	R^2	R^3	X	Time (min)	Yield (%)[b]
1	C_6H_5-	-OEt	$-CH_3$	O	50	92
2	2-Cl- C_6H_4-	-OEt	$-CH_3$	O	60	85
3	4-Cl- C_6H_4-	-OEt	$-CH_3$	O	50	91
4	2-Br- C_6H_4-	-OEt	$-CH_3$	O	60	92
5	2-NO_2- C_6H_4-	-OEt	$-CH_3$	O	90	90
6	3-NO_2- C_6H_4-	-OEt	$-CH_3$	O	80	89
7	4-NO_2- C_6H_4-	-OEt	$-CH_3$	O	90	93
8	4-Me- C_6H_4-	-OEt	$-CH_3$	O	50	96
9	4-OH- C_6H_4-	-OEt	$-CH_3$	O	60	91
10	4-OMe- C_6H_4-	-OEt	$-CH_3$	O	60	94
11	3,4-OMe- C_6H_3-	-OEt	$-CH_3$	O	50	97
12	3,4,5-OMe- C_6H_2-	-OEt	$-CH_3$	O	50	94
13	n-C_3H_7-	-OEt	$-CH_3$	O	60	82
14	C_6H_5-CH=CH-	-OEt	$-CH_3$	O	80	85
15	$N(CH_3)_2$-C_6H_4-	-OEt	$-CH_3$	O	90	84

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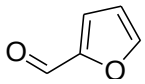
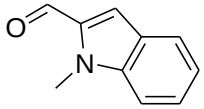
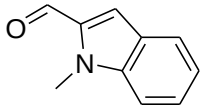
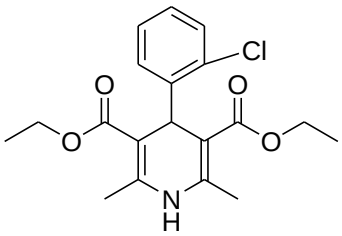
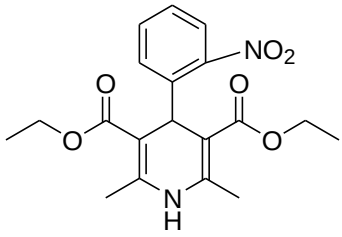
16		-OEt	-CH_3	O	90	84
17		-OEt	-CH_3	O	90	92
18	C_6H_5-	-OEt	C_6H_5-	O	50	90
19	C_6H_5-	-CH_3	-CH_3	O	60	93
20	4-OH- C_6H_4-	-OCH_3	CH_3-O-CH_2-	O	50	95
21		-OCH_3	CH_3-O-CH_2-	O	90	90
22	C_6H_5-	-OEt	-CH_3	S	70	96
23	4-Cl- C_6H_4-	-OEt	-CH_3	S	60	92
24	4-NO_2- C_6H_4-	-OEt	-CH_3	S	70	95
25	4-Me- C_6H_4-	-OEt	-CH_3	S	80	96
26	4-OH- C_6H_4-	-OEt	-CH_3	S	80	92

[a] All the products were well characterized by its ^{1}H NMR, Some of its in ^{13}C NMR, IR, Mass and compared with authentic compounds. [b]Temperature100°C. [c]benzaldehyde (1mmol), Ethyl acetoacetate (1.5 mmol), urea (1.5 mmol), and Ni (II) perchlorate (10 mol%) were used.

In addition with that made attempted to a synthesis of two biologically active compound **Nifedipine and amlodipine.** Its a calcium channel blocker used clinically in the treatment of hypertension and oxygen deficiency diseases of the heart, is synthesized by application of the Hantzch reaction [44].



Amlodipine (27)



Nifedipine (28)

2. RESULTS AND DISCUSSION

The optimum conditions were applied to a series of substituted aromatic, heterocyclic and aliphatic aldehydes. The results are shown in Table 1. Particularly aromatic aldehydes carrying either electron-donating or electron withdrawing substitutions in the ortho, meta and para positions are reacted giving high to excellent yields. With aliphatic aldehydes which normally show extremely poor yields in the Biginelli reaction, gave 42-78% yields of the corresponding dihydropyrimidin-2-(1*H*)-ones **13** (Table 1). The IR spectra of the compounds displayed absorption bands characteristic for the N-H (3207-3290 cm^{-1}) and carbonyl - C = O (1650-1720 cm^{-1}) and 2 - C = O (1588-1682 cm^{-1}) functions, Additionally disubstituted benzene deformation bands were observed in the expected ware number region. In the ^{1}H NMR spectra, the formation of the Octahydroquinazoline skeleton in this reaction was clearly demonstrated by the fact that the C-4 methine proton of compounds appeared at δ 5.0-5.4 ppm on a singlet. The signals of the N_3-H and N_1-H protons of compounds appeared as one-proton singlets at δ 7.2-7.9 ppm and δ 9.3-10.0 ppm respectively.

The proton on N_3-Nitrogen atom might undergo slow exchange and the N_3-H signal was broadened in the compounds by the quadrupolar interaction with nitrogen. The coupling was observed in the signal due to hydrogen on the C-4 atom. The signals of the aliphatic protons of compounds appeared as three-proton singlet and triplet at δ 0.8-1.3 ppm namely C_6 – methyl and carbonyl methyl.

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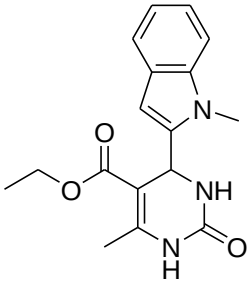

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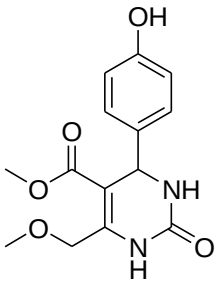

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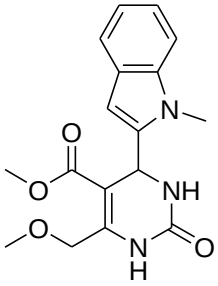

Entry 21

In this work, we used the N-Methyl-indole-2-carbaldehyde and 1,3-dicarbonyl compounds like methoxy methyl acetoacetate. Those are very rarely used in available kinds of literature. The method provides much-improved modification of original Biginelli reaction, in terms of high yield, short reaction time and simple workup procedure and avoid problems associated with solvent use (cost, handling, safety and pollution to the environment). The signals of the methoxy and N-methyl protons of compounds appeared as a three-proton singlet at δ 3.5-3.7 ppm and δ 3.5-3.9 ppm, The signals of the aliphatic protons of compounds appeared as three-proton singlet and triplet at δ 0.8-1.3 ppm. The signals of the aromatic protons of compounds appeared as the multiplet at δ 6.5-8.5 ppm. In the ^{13}C NMR spectra of the compounds are the most deshielded carbon atoms were C_5 (δ 192.45-193.27 ppm) and C2 (δ 152.07-159.15 ppm) appeared. In the EI mass spectra of the compounds, molecular ion peaks $[M]^{+\bullet}$ which appeared at different intensity confirmed the molecular weights of the compounds the base peak was generally formed by the cleavage of the $R^{\bullet}$ or $C_6H_4R^{\bullet}$ radical from the molecular ion.

3. SUMMARY

In summary, we have synthesised economically and environmental friendly dihydropyrimidinones using commercial available Nickel (II) perchlorate by three-component Biginelli condensations of aldehydes with 1,3-dicarbonyl compounds and urea or thiourea under solvent-free conditions with short reaction times. This procedure also suitable for the preparation of calcium channel blocker molecules in a single step and offer several advantages including very good yield.

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