NIso₄ · 7H₂O: Dihydropyrimidin-2(1H)-ones의 One-pot 합성을 위한 효과적이고 환경친화적인 촉매

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NiSO₄ · 7H₂O: An Efficient and Eco-friendly Catalyst for the One-pot Synthesis of Dihydropyrimidin-2(1H)-ones

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INTRODUCTION

The dihydropyrimidinone ring system is contained within a number of pharmacologically active agents, for example, calcium channel blockers, antihypertensive agents, α₁a antagonists, antiviral, antitumor and anti-inflammatory drugs, they have been subject of extensive investigations. In addition, the 2-oxodihydropyrimidine-5-carboxylate core unit is found in nature and in potent HIVgp-120-CD4 inhibitors. Synthetic strategies for the dihydropyrimidinone derivatives would involve one-pot to multistep approaches. The first one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones was reported by Biginelli in 1893, often involves unsatisfactory yields (20-50%), harsh reaction conditions and long reaction times. Although high yields could be achieved by complex multi-step synthesis procedures, these methods lack the simplicity of the original one-pot Biginelli protocol. Therefore, in recent years interest in this reaction has increased rapidly and several modifications and improvements using Lewis acids as well as protic acid under classical reflux, solvent-free conditions and microwave or ultrasound irradiation have been reported. However, in spite of their potential utility, many of these methods involve expensive reagents, strong acidic conditions, long reaction times, high temperatures, stoichiometric amount of catalysts, environmental pollution and give unsatisfactory yields. Therefore, to avoid these limitations, the discovery of a new and efficient catalyst with high catalytic activity, short reaction time and simple work-up for the preparation of 3,4-dihydropyrimidin-2(1H)-ones under neutral, mild and practical conditions is of prime interest. In view of increasing environmental constraints, it has become unacceptable for industrial effluents and wastes to contain such a highly toxic transition metal. The design of new, less polluting procedures has become a priority for the chemical industry. Recently, NiSO₄·7H₂O has been used as a Lewis acid catalyst for organic transformation. It is an inexpensive, available and extremely safe reagent to be used in chemical reactions.

In continuation of our work to develop new synthetic methodologies, we describe herein an efficient and convenient procedure for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones or thiones in the presence of a catalytic amount of nickel(II).
sulfate heptahydrate in acetonitril (Scheme I).

RESULT AND DISCUSSION

According to results, we discovered a practical and general approach for this Biginelli cyclocondensation reaction using a mild catalyst, nickel(II) sulfate heptahydrate which is a novel, one-pot combination of nickel(II) sulfate heptahydrate and proton source that not only preserved the simplicity of Biginelli’s one-pot reaction but also consistently produced 70-80% yields of the 3,4-dihydropyrimidin-2(1H)-ones or thiones (Table 1).

In order to study the generality of this procedure, a series of Biginelli compounds were synthesized with similar operations. Under this novel conditions, the reaction time was significantly shorted from 18h of the classical Biginelli method to 2h, and the yields

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>X</th>
<th>Product</th>
<th>Time (h)</th>
<th>Mp(°C)</th>
<th>Yield (%)</th>
</tr>
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<tr>
<td>1</td>
<td>Ph</td>
<td>O</td>
<td>4a</td>
<td>1.5</td>
<td>202-204</td>
<td>80</td>
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<tr>
<td>2</td>
<td>4-Me-Ph</td>
<td>O</td>
<td>4b</td>
<td>1.5</td>
<td>213-214</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>4-MeO-Ph</td>
<td>O</td>
<td>4c</td>
<td>1.5</td>
<td>199-202</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>4-NO₂-Ph</td>
<td>O</td>
<td>4d</td>
<td>1.5</td>
<td>209-210</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>4-Cl-Ph</td>
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<td>4e</td>
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<td>215-216</td>
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</tr>
<tr>
<td>6</td>
<td>3-NO₂-Ph</td>
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<td>4f</td>
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<td>S</td>
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<td>4-Cl-Ph</td>
<td>S</td>
<td>4h</td>
<td>1.5</td>
<td>208-209</td>
<td>77</td>
</tr>
</tbody>
</table>

*Isolated yields.
increased from 20-50% to 70-80%. Most importantly, aromatic aldehydes carrying either electron donating or withdrawing substituents afforded good yields of products. Furthermore, thiourea has been used with similar success to provide the corresponding 3,4-dihydropyrimidin-2(1H)-thiones which are possessing good biological activities. In order to get the best molar ratio of reaction materials, we also the experiment with different ratios of aldehyde(1), ethylacetoacetate(2), urea or thiourea(3) and nickel(II) sulfate heptahydrate. We found that the reaction gave the best results when the molar ratio of reactions was 1(1): 1(2): 1.5(3): 0.05(catalyst), respectively.

We propose a mechanism similar to that of Kappe for the Biginelli reaction and established that the first step in this reaction involves the acid-catalyzed formation of acyl imine intermediate 6, formed by reaction of the aldehyde with urea and stabilized by nickel, is the key rate-limiting step. Intercetation of the iminium ion 6 by β-ketoester enolate produce an open-chain ureide 7 which subsequently cyclizes to the dihydropyrimidinones, 4 (Scheme II).

To show the merits and advantages of using NiSO₄.7H₂O as a catalyst, our method is compared with reported Biginelli reactions (Table 2).

In conclusion, we have developed a catalytic system for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones or thiones using available, inexpensive and extremely safe reagent such as nickel(II) sulfate heptahydrate in the mild and high yielding reaction. The catalyst can be recycled at three times without significant lose of catalytic activity. We believe nickel(II) sulfate heptahydrate is the greenest catalyst which has ever been used for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones or thiones will find many applications in organic synthesis and industry.

**EXPERIMENTAL**

All products are known compounds and were characterized by mp, IR, ¹H NMR and GC/MS. Melting points were measured by using the capillary tube method with an electrothermal 9200 apparatus. ¹H NMR spectra were recorded on a Bruker AQS ADVANCE-300 MHz spectrometer using TMS as an internal standard (CDCl₃ solution). IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27. GC/MS spectra were recorded on an Agilent Technologies 6890 network GC system and an Agilent 5973 network Mass selective detector. Thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel, 60 F254 was used to monitor the progress of reactions. All products were characterized by spectra and physical data.

**General procedure for the synthesis of 4-aryl-3,4-dihydropyrimidin-2(1H)-one or thione**

A mixture of aldehyde (2 mmol), ethyl acetoacetate (2 mmol), urea or thiourea (3 mmol) and NiSO₄.7H₂O (0.1 mmol) in 5 mL CH₃CN were refluxed for 2 h. The mixture was cooled to room temperature. After filtration, the solution poured into ice-water (30 mL). The resulting solid product was then removed by filtration and recrystallized from absolute ethanol to give pure product.

**5-Ethoxycarbonyl-4-phenyl-6-methyl -3,4-dihydropyrimidin-2(1H)-one (4a)**

Mp 200-202°C; IR (KBr) (v̇max, cm⁻¹): 3244, 1724, 1639; ¹HNMR (CDCl₃, 300 MHz) δH (ppm): 1.1 (t,
3H, CH₃* CH₂O), 2.24 (s, 3H, CH₃), 4.01 (q, 2H, OCH₂), 5.16 (s, 1H, CH), 7.21-7.30 (m, 5H, aromatic CH), 7.76 (s, 1H, NH), 9.24 (s, 1H, NH); GC/Ms: 260 (M⁺).

5-Ethoxycarbonyl-4(4-nitro-phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (4d)

Mp 209-210°C; IR (KBr) (νmax, cm⁻¹): 3250, 1720, 1636; ¹HNMR (CDCl₃, 300 MHz) δH (ppm): 1.1 (t, 3H, CH₃* CH₂O), 2.24 (s, 3H, CH₃), 4.01 (q, 2H, OCH₂), 5.16 (s, 1H, CH), 7.21-7.30 (m, 5H, aromatic CH), 7.76 (s, 1H, NH), 9.24 (s, 1H, NH); GC/Ms: 260 (M⁺).

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REFERENCES