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Electronegativity Impact on metal (Copper, Iron, Zinc) Lewis acid catalysts in the Biginelli Reaction: A Comparative Study

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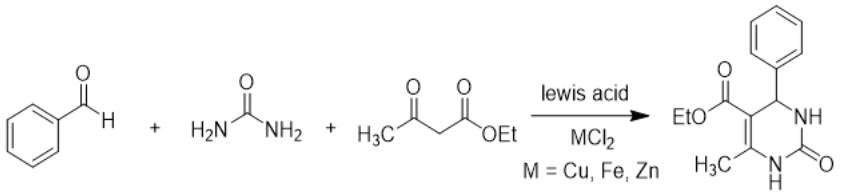
Abstract:

The Biginelli reaction is a very practical multi-component reaction, and the products 3,4-Dihydropyrimidine-2(1H)-ones (DHPMs) play an important role in the pharmacy scope. Herein, $CuCl_2$, $FeCl_3$, and $ZnCl_2$ were used to investigate the catalytic activity differences among these metal Lewis acid catalysts for the Biginelli reaction under controlled conditions. Based on reaction mechanism, we believe that highly electronegative metals are beneficial for activating imines and enol intermediates, thereby increasing reaction yields.

Keywords: Biginelli reaction, Metal Lewis acid catalysts, Electronegativity, Catalytic activity

Introduction

The Biginelli reaction is a well-known and remarkable multi-component reaction (MCR) that was first reported in 1893 by Pietro Biginelli, an Italian chemist[1]. This reaction yields 3,4-Dihydropyrimidine-2(1H)-ones (DHPMs) derivatives, an important family of heterocyclic compounds. In the past twenty years, DHPMs have attracted significantattention in medicinal chemistry due to their biological activity, such as active components or precursors for medicines with antifungal, anti-inflammatory, antitumoral (Eg5), and antibacterial activities[2–5]. Therefore, DHPMs sparked considerable research interest in the field of drug design and synthesis including new pyrimidine derivatives comprising arylsulfonylhydrazino, ethoxycarbonylhydrazino, thiocarbamoylhydrazino and substituted hydrazone, and thiosemicarbazide functionalities[6]. Moreover, these compounds are commonly used in research to explore new pharmacological mechanisms of action and potential therapeutic targets[7]. Thanks to the latest research finding that either Multi-Target-Directed Ligands (MTDLs) or monotarget compounds have been developed by MCRs to address different factors implicated in the treatment of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease[8], the Biginelli reaction has once again been pushed to the forefront and become a hot spot[9]. Many efforts have been taken to enhance the efficiency, selectivity, and environmental sustainability of this reaction by ongoing methodology exploration, such as different catalytic systems, and substrate scope. Recent studies include microwave irradiation[10], ionic liquids as homogeneous and heterogeneous catalysts[11,12], ultrasound irradiation[13], etc. After extensive research, chemists have investigated that Lewis acids, including $ZnCl_2$[14], CuI[15], $BiCl_3$[16], $CuBr_2$[17], CuCl[18], $NiCl_2{\cdot}6H_2O$[19], or $NiBr_2$[20], have the ability to effectively catalyze this reaction. Although various new catalysts have been developed, few works have been done to disclose the origin of catalytic activity difference between the catalysts such as $CuCl_2$, $ZnCl_2$, and $FeCl_3$, which are fourth-period metal Lewis acid. Hence our study examines the catalytic efficacy of $CuCl_2$, $ZnCl_2$, and $FeCl_3$, for the Biginelli reaction. Under controlled conditions, such as same reaction time, temperature, solvent, and reactant molar ratio. Among the three Lewis catalysts, $CuCl_2$ gave the highest yield of 83% than 72% of $FeCl_3$ and 14% of $ZnCl_2$. Based on reaction mechanism analysis, we believe that highly electronegative metals are beneficial for activating imines and enol intermediates, which consistent with the results.



Scheme 1. Biginelli reaction of benzaldehyde, urea and ethyl acetoacetate

Results and discussions

We used a template reaction of benzaldehyde, urea and ethyl acetoacetate (molar ratio 1:1.1:1.2) to investigate the differences in catalytic activity of $CuCl_2$, $FeCl_3$, and $ZnCl_2$ Lewis acid catalyst (10mol%) for the Biginelli reaction. As show in Table 1, under controlled conditions, using ethanol as the solvent and reflux for 3 hours, the reaction synthesized DHPM product with isolated yields of 83%, 72% and 14%, respectively.

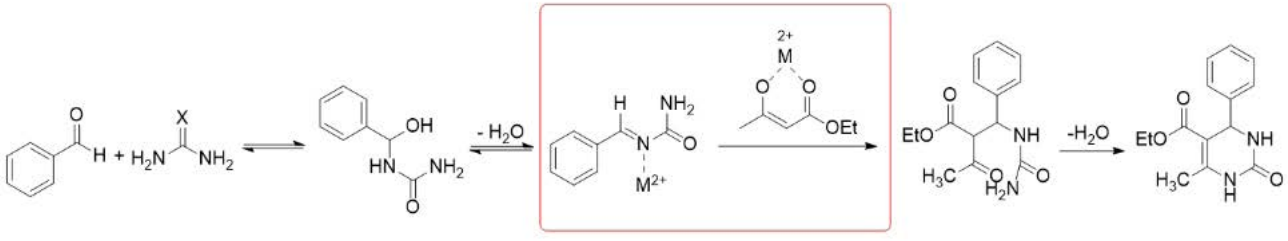
Table 1. Biginelli reactions catalyzed by $CuCl_2$, $FeCl_3$, and $ZnCl_2$ Lewis acid catalysts[a]

Entry	Catalyst (10mmol%)	Solvent	Time (min)	Temperature (^oC)	Yield[b] (%)
1	$CuCl_2$	Ethanol	180	100 (reflux)	83
2	$FeCl_3$	Ethanol	180	100 (reflux)	72
3	$ZnCl_2$	Ethanol	180	100 (reflux)	14

a. All the reactions were performed with benzaldehyde (10.0 mmol), ethyl acetoacetate (11.0mmol), urea (12.0mmol), and catalyst (10.0 mmol) in refluxing ethanol (20 mL) at 100 ^oC.

b. Isolated yields.

Analyzing reaction mechanism could help us to investigate the difference in catalytic activity of the above Lewis acid catalyst. Scheme 2 show the popular mechanism of the Lewis acid catalyzed Biginelli reaction[21,22]. After benzaldehyde reacts with urea to form imine, the nitrogen of imine complexes with the Lewis acid metal ion, in which the metal ion reduces the charge density and makes the imine more electrophilic. The Lewis acid catalyst also chelate with the two carbonyl groups of ethyl acetoacetate to facilitate enolization and make ethyl acetoacetate more nucleophilic. Finally, the nucleophilic ethyl acetoacetate enol reacts with the electrophilic imine to form a product after dehydration. The combination of an electron-poor Lewis acid catalyst with the nitrogen atom helps the imine to be attacked by nucleophilic reagents, and the combination of the catalyst with ethyl acetate could improve the nucleophilicity of enols. For instance, zinc has an electronegativity of 1.65, which give 14% yield, lower than 72% of Iron (III) with an electronegativity of 1.83. Copper with the highest electronegativity of 1.90 and give highest yield of 83%. These yield results seem to agree with the order of increasing electronegativity. Therefore, we believe that the catalytic ability is related to electronegativity of the metal, highly electronegative metals are beneficial for activating imines and enol intermediates.



Scheme 2. Mechanism of Lewis acid catalyzed Biginelli reaction

Conclusion

In order to explore the impact of Lewis metal catalysts on the Biginelli reaction, $CuCl_2$, $FeCl_3$, and $ZnCl_2$ were used to investigate the catalytic activity differences for this reaction under controlled conditions. Among the three metal Lewis acid catalysts, $CuCl_2$ gave the highest yield of 83% than 72% of $FeCl_3$ and 14% of $ZnCl_2$. We believe that metals' electronegativity plays a crucial role in determining catalytic efficiency. The higher metal electronegativity displays better catalytic ability. These findings not only contribute to a deeper understanding of the Biginelli reaction mechanism but also provide valuable insights for the development of more efficient and sustainable MCRs.

Experimental

All the reactions were performed with benzaldehyde (10.0 mmol), ethyl acetoacetate (11.0mmol), urea (12.0 mmol), and metal Lewis acid catalyst (1.0 mmol, 10mmol%) in refluxing ethanol (20 mL) at 100 °C for 3h with stirring in an 100ml flask. After cooling, the reaction mixture was poured into ice water mixture (100g) and stirred for 90 min. The separated solid was filtered under suction for 90 min. Finally used ethanol to recrystallize and dry to constant weight. The results are summarized in Table 1.

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