

Comparative study on Lewis acid catalyzed Biginelli reaction for the synthesis of 3,4-dihydropyrimidin-2(1H)-thione

Yiyang Liu,

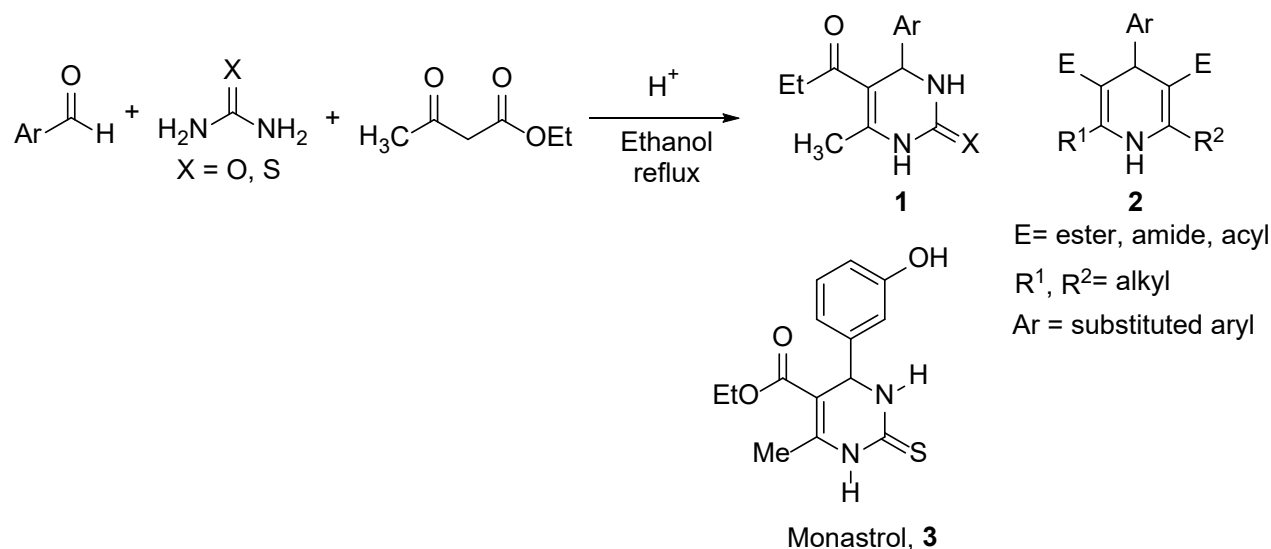
Whartonn School in Chengdu
Sichuan P.R.C.
No. 45, Xinshang Road, Wuhou
District
9127881@qq.com

Abstract:

One-pot condensation reaction of an aromatic aldehyde, urea/thiourea and ethyl acetoacetate yielding 3,4-dihydropyrimidin-2(1*H*)-ones (DHPPM) is known as the Biginelli reaction or Biginelli condensation. The corresponding thione derivatives are also of much interest for high biological activity. However, there are few examples of Lewis acid catalyzed synthesis of thiones in methodological research, and the product yields are relatively low. In order to explore the reasons for the differences in activity of different types of catalysts for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-thiones, we chose $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$, $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ and TsOH(*p*-Toluenesulfonic acid) for comparative study. Experimental results show that $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ has the best yield of 50.3 % higher than 6.2 % and 0.7 % of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ and $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$, respectively. The reason for the decrease in catalytic activity may be due to the increased coordination strength between the catalyst and the sulfur atoms in thiourea.

Keywords: Biginelli reaction, 3,4-Dihydropyrimidin-2(1*H*)-thione, Lewis acid catalyst, Catalytic activity

Introduction



Scheme 1. Biginelli reaction of benzaldehyde, urea and ethyl acetoacetate for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones (DHPM, 1), the structure of compound 2 and monastrol (3).

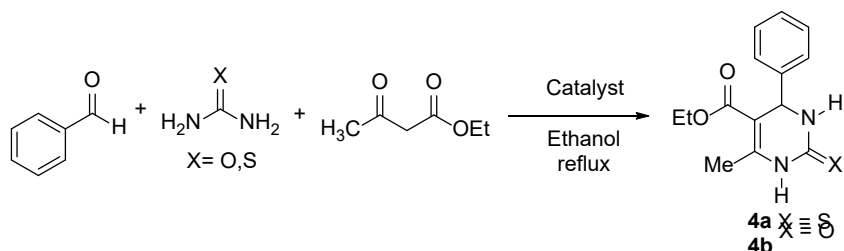
In 1893, Biginelli reported the first synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones (DHPM, compound 1, Scheme 1) by a very simple one-pot condensation reaction of an aromatic aldehyde, urea and ethyl acetoacetate [1]. This synthesis method is known as the Biginelli reaction or Biginelli condensation. Until the early 1980s, that pyridine compound 2, similar in structure to compound 1, was discovered to exhibit calcium antagonistic activity [2]. This discovery sparked renewed interest in the pharmacological properties of DHPM compounds, revealing their calcium antagonistic, antihypertensive, antitumor, and other activities [3]. Consequently, the study of the Biginelli reaction has garnered a great deal of attention [4]. Beyond its reaction mechanism, research efforts have increasingly focused on exploring and refining the reaction conditions, as well as synthesizing a variety of products. A range of Lewis acid catalysts such as $\text{BF}_3 \cdot \text{OEt}_2$, FeCl_3 , $\text{Yb}(\text{OTf})_3$, $\text{Cu}(\text{OTf})_2$, LiBr , InX_3 , BiCl_3 , $\text{Mn}(\text{OAc})_3$, LiC-IO_4 , $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ and $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ have been continuously incorporated into this reaction, significantly expanding the

use of three key reaction materials: ketone esters, aromatic aldehydes, and urea/thiourea [5]. Due to their biological activity, the corresponding thione derivatives are also of much interest. For example, monastrol (3) has been also found to be a mitotic kinesin Eg5 motor protein inhibitor and considered as a potential new lead compound for the anticancer drug development [6].

We have noticed that there are few examples of Lewis acid catalyzed synthesis of thiones in methodological research, and the product yields are relatively low. In order to explore the reasons for the differences in activity of different types of catalysts for the synthesis of thiones, we chose $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$, $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ and TsOH (p-Toluenesulfonic acid) for comparative study.

Experimental

All the reactions were performed with benzaldehyde (10.0 mmol), ethyl acetoacetate (10.0 mmol), thiourea (11.0 mmol), and metal Lewis acid catalyst (1.0 mmol, 10 mmol%) in refluxing ethanol (20 ml) at 100 °C for 5hr with stirring in an 100ml flask. After cooling, the reaction mixture was poured into ice water mixture (100 g) and stirred for 10 min. The separated solid was filtered under suction for 10 min. Collected filter cake and air dry until constant weight. The results are summarized in Table 1.

Table 1. Biginelli reactions catalyzed by different type of catalysts^a

Entry	Catalyst (10 mmol%)	X	Yield ^b (%)
1	CuCl ₂ ·2H ₂ O	S	6.2
2	CoCl ₂ ·6H ₂ O	S	0.7
3	NiCl ₂ ·6H ₂ O	S	50.3
4	TsOH	S	34.9
5	CuCl ₂ ·2H ₂ O	O	57.7
6	CoCl ₂ ·6H ₂ O	O	65.8

a. All the reactions were performed with benzaldehyde (10.0 mmol), ethyl acetoacetate (10.0 mmol), urea (11.0 mmol), and catalyst (1.0 mmol) in refluxing ethanol (20 ml) at 100 °C for 6 hr.

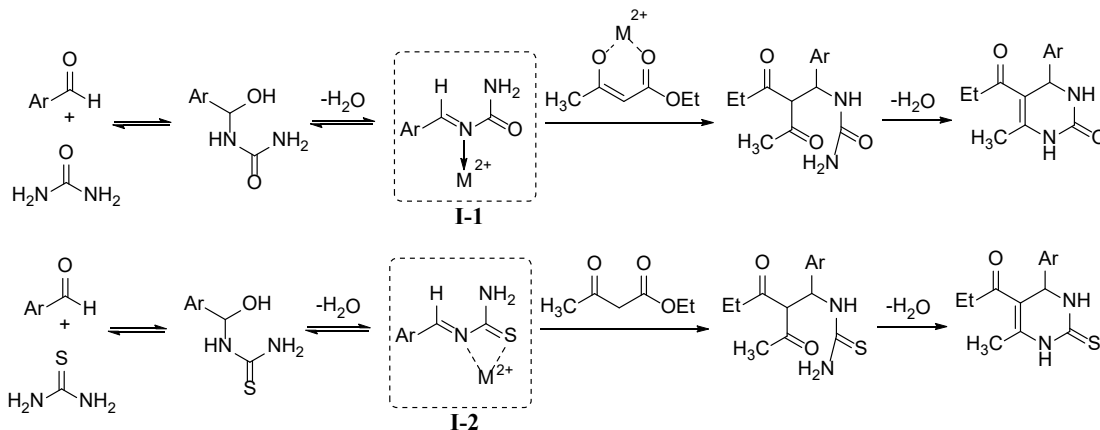
b. Isolated yields.

Results and discussion

We used a template reaction of benzaldehyde, ethyl acetoacetate and thiourea (molar ratio 1:1:1.1) to investigate the differences in catalytic activity of CuCl₂·2H₂O, CoCl₂·6H₂O and NiCl₂·6H₂O Lewis acid catalyst (10 mol%) for the Biginelli reaction. As shown in Table 1, under controlled conditions, using ethanol as the solvent and reflux for 6 hours, the reaction synthesized 3,4-dihydropyrimidin-2(1*H*)-thione product 4a with isolated yields of 6.2 %, 0.7 % and 50.3 % (entry 1–3), respectively. Under the same reaction conditions, catalyzed by TsOH, the yield of

4a was 34.9 % (entry 4), which may be caused by its weak acidity. When CuCl₂·2H₂O and CoCl₂·6H₂O were used to catalyze the Biginelli reaction involving urea, the yields of the corresponding product 4b were 57.7% and 65.8% (entry 5 and 6), respectively, which were significantly higher than the yield of synthesized product 4a. The results of the above comparative experiments indicate that there are significant differences in the catalytic activity of the same catalyst in Biginelli reactions involving urea versus thiourea.

Analyzing reaction mechanism could help us to investigate the difference in catalytic activity of the above Lewis acid catalyst, CuCl₂·2H₂O, CoCl₂·6H₂O and NiCl₂·6H₂O. Scheme 2 depicted the popular mechanism of the Lewis acid catalyzed Biginelli reaction using aromatic aldehyde, urea/thiourea and ethyl acetoacetate as substrates [7–10].



Scheme 2. Mechanism of Lewis acid catalyzed Biginelli reaction

In the Biginelli reaction involving urea, urea reacts with aromatic aldehydes to dehydrate and form imines. Metal

ions catalyze the reaction by activating imine (intermediate I-1) and enolized ethyl acetate. Whereas in the reaction involving thiourea, we believe that the nitrogen and sulfur atoms of imines coordinate with metal ions in $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ or $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ catalysts to form intermediate I-2. Due to the varying coordination abilities of different metal ions, the catalytic activity is affected. From the performance of the three different catalysts, the coordination effect of Co^{2+} is the strongest, making it unable to activate ethyl acetoacetate, resulting in the lowest catalytic activity. The coordination between Ni^{2+} and imines is the weakest, therefore the catalytic activity of $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ is the highest.

Conclusion

This article conducted a comparative study on the catalytic activity differences of three different catalysts for the synthesis of 3,4-dihydropyrimidin-2(1H)-thiones through the one-pot Biginelli reaction. Experimental results show that $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ has the best yield of 50.3 % higher than 6.2 % and 0.7 % of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ and $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$, respectively. Based on the analysis of the reaction mechanism, the variation in catalytic activity may be attributed to the differing strengths of coordination between metal ions and the N, S atoms of the imine intermediates. Co^{2+} exhibits the strongest coordination effect, consequently restricting their ability to activate the enol form of ethyl acetoacetate. As a result, its catalytic activity is the lowest.

References

- [1] Biginelli, P. Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones, *Gazz. Chim. Ital.* 1893, 23, 360–366.
- [2] Atwal, K. S.; Rovnyak, G. C.; Kimball, S. D.; Floyd, D. M.; Moreland, S.; Swanson, B. N.; Gougoutas, D. Z.; Schewartz, J.; Smillie, K. M.; Malley, M. F. Dihydropyrimidine Calcium Channel Blockers. II. 3-Substituted-4-aryl-1,4-dihydro-6-methyl-5-pyrimidinecarboxylic Acid Esters as Potent Mimics of Dihydropyridines, *J. Med. Chem.* 1990, 33, 2629–2635.
- [3] (a) Nagarathnam, D.; Miao, S.W.; Lagu, B.; Chiu, G.; Fang, J.; Murali Dhar, T. G.; Zhang, J.; Tyagarajan, S.; Marzabadi, M. R.; Zhang, F.; Wong, W. C.; Sun, W.; Tian, D.; Zhang, J.; Wetzel, J. M.; Forray, C.; Chang, R. S. L.; Broten, T. P.; Schorn, T. W.; Chen, T. B.; O'Malley, S.; Ransom, R. W.; Schneck, K.; Bendesky, R.; Harrell, C. M.; Gluchowski, C. Design and Synthesis of Novel α_{1a} Adrenoceptor-Selective Antagonists. 1. Structure-Activity Relationship in Dihydropyrimidinones, *J. Med. Chem.* 1999, 42, 4764–4777. (b) Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; Brossi, C. D.; Mai, S.; Trunch, A.; Faulkner, D. J.; Carte, B.; Breen, A. L.; Hertzberg, R. P.; Johnson, R. K.; Westly, J. W.; Potts, B. C. M.; Novel Alkaloids from the Sponge *Batzella* sp.: Inhibitors of HIV gp120-Human CD4 Binding, *J. Org. Chem.* 1995, 60, 1182–1188. (c) Kappe, C. O.; Fabian, W. M. F.; Semones, M. A. Conformational Analysis of 4-Aryldihydropyrimidine Calcium Channel Modulators. A Comparison of Ab Initio, Semiempirical and X-Ray Crystallographic Studies, *Tetrahedron* 1997, 53, 2803–2816.
- [4] Kappe, C.O. 100 Years of the Biginelli dihydropyridine synthesis, *Tetrahedron* 1993, 49, 6937–6963.
- [5] Heravi, M. M.; Zadsirjan, V. Recent Advances in Biginelli-type Reactions, *Curr. Org. Chem.* 2020, 24, 1331–1366.
- [6] Mayer, T. U.; Kapoor, T. M.; Haggarty, S. J.; King, R. W.; Schreiber, S. L.; Mitchison, T. J. Small Molecule Inhibitor of Mitotic Spindle Bipolarity Identified in A Phenotype-based Screen, *Science* 1999, 286, 971–974.
- [7] Kappe C. O. A Reexamination of the Mechanism of the Biginelli Dihydropyrimidine Synthesis. Support for an N-Acyliminium Ion Intermediate, *J. Org. Chem.* 1997, 62, 7201–7204.
- [8] Kappe C. O. Recent Advances in the Biginelli Dihydropyrimidine Synthesis. New Tricks from an Old Dog, *Acc. Chem. Res.* 2000, 33, 879–888.
- [9] Costanzo, P.; Nardi, M.; Oliverio, M. Similarity and Competition between Biginelli and Hantzsch Reactions: An Opportunity for Modern Medicinal Chemistry, *Eur. J. Org. Chem.* 2020, 3954–3964.
- [10] Lu, J.; Bai, Y. J.; Guo, Y. H.; Wang, Z. J.; Ma, H. R. $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ or $\text{LaCl}_3 \cdot 7\text{H}_2\text{O}$ Catalyzed Biginelli Reaction. One-Pot Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones, *Chin. J. Chem.* 2002, 20, 681–687.