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Novel Biginelli-like three-component cyclocondensation reaction: efficient synthesis of 5-unsubstituted 3,4-dihydropyrimidin-2(1*H*)-ones

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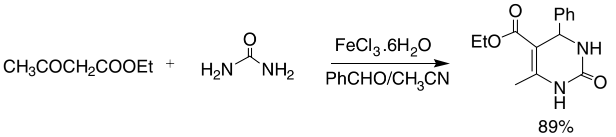
Abstract—Iron (III) catalyzed the three-component Biginelli-like cyclocondensation reaction efficiently in acetonitrile to afford the corresponding 5-unsubstituted 3,4-dihydropyrimidin-2-(1*H*)-ones in high yields. The first Biginelli-like reactions of urea, aldehydes and ketones were furnished important new 3,4-dihydropyrimidin-2-(1*H*)-ones derivatives suitable for further study.

There is considerable current interest in the Biginelli reaction, because 3,4-dihydropyrimidin-2-(1*H*)-ones and their derivatives have attracted great attention recently in synthetic organic chemistry due to their pharmacological and therapeutic properties such as antibacterial and antihypertensive activity as well as behaving as calcium channel blockers, α-1a-antagonists and neuropeptides Y (NPY) antagonists.[1] The Biginelli reaction is one of the multicomponent reactions (MCRs) and the most important procedures for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones. In general, Biginelli reactions are simple one-pot but low-yielding condensations of β-dicarbonyl compounds with aldehydes and urea, and strong acids and Lewis acids such as $BF_3{\cdot}OEt_2$, $LaCl_3$, $La(OTf)_3$, $Yb(OTf)_3$, InX (X = Cl, Br), $ZrCl_4$, $BiCl_3$, $LiClO_4$, etc. have been employed for this transformation (Scheme 1).[2,3] However, many of these reagents or catalysts are expensive, harmful and difficult to handle especially on a large scale.



Scheme 1. Biginelli reaction catalyzed by $FeCl_3{\cdot}6H_2O$.

Previous reported protocols normally required prolonged reaction times and high temperature with moderate yields, so there has been considerable interest to explore mild, rapid, and higher yielding protocol at ambient temperature. In continuation of interest in the use of Lewis acid catalyst or reagent[4] and our interest in the preparation of new 3,4-dihydropyrimidin-2-(1*H*)-ones derivatives led us to attempt the extension of this versatile reaction to other substrates.

At first, we found the Biginelli reaction of acetoacetate, benzylaldehyde and urea could be catalyzed by $FeCl_3{\cdot}6H_2O$ in the absence of any additives, and the desired product was obtained in high yield under reflux for 3h (89%). The good results prompted us to investigate new substrate for the extension of this versatile Biginelli reaction Leading directly to 5-unsubstituted 3,4-dihydropyrimidin-2(1*H*)-ones. At present, there are few articles describing the synthesis of certain 5-unsubstituted 3,4-dihydropyrimidin-2(1*H*)-ones.[5] And previous reported methods have typically accomplished the synthesis of 5-unsubstituted dihydropyrimidinones in a multistep fashion via the saponification of the C-5 ester on the preassembled pyrimidinone followed by thermal decarboxylation.[6,7] These harsh and inefficient methods have

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Keywords: Three component; Biginelli-like reaction; Cyclocondensation; One pot; Iron.

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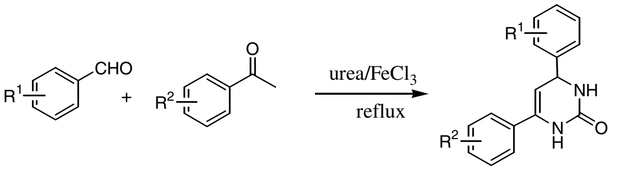


Scheme 2. Biginelli-like reaction.

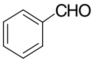
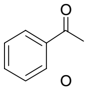
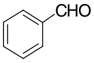
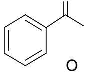
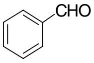
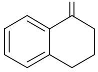
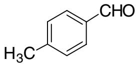
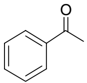
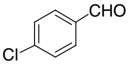
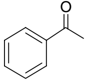
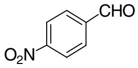
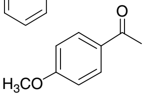
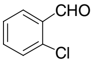
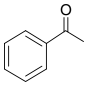
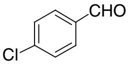
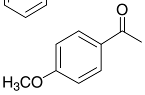
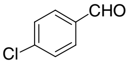
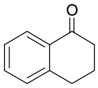
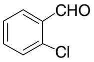
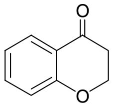
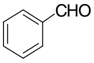
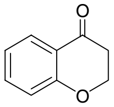
resulted in low-yielding transformations and multiple side products.

The use of ketones gave us the opportunity to prepare corresponding new 5-unsubstituted 3,4-dihydropyrimidin-2-(1*H*)-ones derivatives (Scheme 2). And the Biginelli-like reactions of ketones with single carbonyl group provide a useful 5-unsubstituted 3,4-dihydropyrimidin-2-(1*H*)-ones. Herein we continued to describe a simple and efficient protocol for the Biginelli-like three-component cyclocondensation reactions of aldehydes, ketones and urea for the synthesis of 5-unsubstituted 3,4-dihydropyrimidin-2-(1*H*)-ones using very cheap $FeCl_3{\cdot}6H_2O$ under mild conditions.

In the primary study, we found only $FeCl_3{\cdot}6H_2O$ used as catalyst in this reaction gave few products. However, the addition of TMSCl accelerated the Biginelli-like reaction and gave good results. For example, the TMSCl-mediated Biginelli-like reaction of acetophenone, benzaldehyde, and urea gave corresponding product in high yield at reflux for 12 h (Table 1, entry 1). The role of TMSCl is not completely understood, it may be explained in terms of hard–soft acid, which activates the carbonyl group (ketone).[8]

Then the Biginelli-like reactions of other various aldehydes and ketones were general run under established protocol wherein we used a 1:1:1.5 ratio of ketones, aldehyde, and urea, respectively. After the completion of the reaction, as indicated by TLC, and the crude products were directly filtrated through a sintered funnel. The crude product was further purified by recrystallization (EtOH) to afford products as indicated in Table 1. In all cases studied, the three-component reaction proceeded smoothly to give the corresponding 5-unsubstituted 3,4-dihydropyrimidin-2-(1*H*)-ones in high yields. Especially, aromatic aldehydes carrying either electron-donating or electron-withdrawing substitutents reacted efficiently to give good yields. Although TMSCl was used as additive, the three-component cyclocondensation products were generally obtained in good yields under mild conditions.

Table 1. Iron catalyzed three-component Biginelli-like cyclocondensation reaction[9]

Entry[a]	Aldehydes	Ketones	Yield[b]/%
1			82
2			0[c]
3			86
4			83
5			88
6			86
7			78
8			85
9			89
10			75
11			81

[a] Reaction conditions: aldehyde (1 mmol), urea (1.5 mmol), and ketones (1 mmol) in CH_3CN (3 mL), $FeCl_3{\cdot}6H_2O$ (0.1 mmol), TMSCl (1 mmol), reflux, 12 h.

[b] Isolated yield.

[c] At room temperature.

In summary, a mild, convenient method for the three-component Biginelli-like reactions in the presence of $FeCl_3{\cdot}6H_2O$ catalyst has been discovered. We expanded the synthetic scope of the multicomponent Biginelli-like three-component cyclocondensation reaction to ketones other than activated β-dicarbonyl compounds (acetoacetate) for the synthesis of interesting 5-unsubstituted 3,4-dihydropyrimidin-2-(1*H*)-ones. These results not only provide a new aspect of catalytic organic reaction catalyzed by $FeCl_3{\cdot}6H_2O$ but also extend the utility of ketones in Biginelli reactions.

Acknowledgements

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9. *General procedure for the Biginelli-like reaction catalyzed by* $FeCl_3\cdot 6H_2O$: To a solution of aldehyde (1.0 mmol) and $FeCl_3\cdot 6H_2O$ (0.1 mmol, 10 mol%) in CH_3CN (3 mL) was added urea (1.5 mmol), ketone (1.0 mmol), and TMSCl (1.0 mmol) successively. And the reaction mixture was refluxed until the reaction reached completion, as evidenced by TLC. After completion of the reaction, the mixture was added with water, and the crude products were directly filtrated through a sintered funnel. The crude product was further purified by recrystallization (EtOH) to afford products as indicated in Table 1. All the products were identified by NMR (Varian INOVA-400) and GC–MS (Agilent 6890N GC/5973N MS, HP-5MS).