

Si-Fe Catalyzed Biginelli Reaction : A Versatile Method for the Synthesis of Dihydropyrimidinones

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ABSTRACT

Dihydropyrimidinones were prepared involving Biginelli reaction of various aldehydes, urea/thiourea and ethyl acetoacetate in the presence of a heterogeneous Si-Fe catalyst.

Keywords : Biginelli Reaction, Multicomponent Reactions, Si-Fe Catalyst, Dihydropyrimidinone.

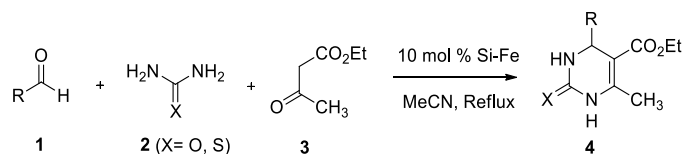
I. INTRODUCTION

Acid catalyst Biginelli reaction is a versatile route for the synthesis of dihydropyrimidinones.¹⁻³ It is very useful intermediate having biological activity e.g. calcium channel blocker, antihypertensive, α -antagonist, antibacterial, antiviral antitumor, anti-inflammatory and HIV agents.⁴⁻⁵ The several reports are available for the synthesis of dihydropyrimidinone by using acid catalyst like Conc. HCl, $\text{BF}_3 \cdot (\text{OEt})_2$, Clay, InCl_3 , LaCl_3 , Lanthanide triflate, H_2SO_4 , ceric ammonium nitrate, $\text{Mn}(\text{OAc})_3$, ion-exchange resin, 1-*n*-butyl-3-methyl imidazolium tetra fluoroborate, BiCl_3 , LiClO_4 , InBr_3 , FeCl_3 , ZnCl_4 , $\text{Cu}(\text{OTf})_2$, $\text{Bi}(\text{OTf})_3$, LiBr, ytterbium triflate, NH_4Cl , MgBr_2 and other reagents have been used for this transformation.⁶⁻²⁵ Due to their wide range of activity and importance, a simple and high yielding one-pot approach for the synthesis of dihydropyrimidinones is highly desirable.

Heterogeneous systems have tremendous advantages over homogeneous ones and through heterogenizing the catalysts of the reagents certain practical limitations of homogeneous systems can be eliminated. One of the most attractive advantages of heterogeneous systems is the easy separation and facile recovery of the solid catalyst from the products for recycling without tedious experimental workup. A simple, efficient and environment friendly, one-pot synthesis of dihydropyrimidinones by direct condensation of aromatic aldehyde with acetoacetate esters and urea was undertaken using catalytic amount of Si-Fe complex.

II. RESULTS AND DISCUSSIONS

In continuation with our efforts to develop the new methods for the synthesis of bioactive organic compounds,²⁶ we have developed a new method for the synthesis of dihydropyrimidinone derivatives using heterogeneous Si-Fe catalyst in acetonitrile (**Scheme 1**). Si-Fe catalyst is prepared by using reported procedure in literature.²⁷ The reaction of benzaldehyde **1**, urea/thiourea **2** and acetoacetate **3** has been carried out in the presence of Si-Fe as a catalyst.



Scheme 1. Synthesis of dihydropyrimidinone derivatives

The generality of this method was examined by the reaction of several substituted aldehyde, acetoacetate and urea/thiourea using Si-Fe catalyzed in acetonitrile. The results are shown in **Table 1**. We have carried out similar reactions with various aldehydes **1** (1 mmol) with acetoacetate (1 mmol) and urea/thiourea (1.5 mmol) in the presence of Si-Fe catalyst (10 mol %). All the products obtained were confirmed by spectroscopic methods such as IR, ^1H NMR comparing with reported in literature.

Table 1. Si-Fe catalyzed synthesis of dihydropyrimidinone derivatives.

Entry	R	X	Time (hr)	Yield (%)
4a	Ph	O	18	90
4b	CH ₃	O	16	88
4c	CH ₃ -CH ₂	O	18	85
4d	CH ₃ -CH ₂ -CH ₂	O	18	90
4e	4-(NO ₂)-C ₆ H ₄	O	18	80
4f	4-(Cl)-C ₆ H ₄	O	20	85
4g	Ph-CH=CH	O	18	90
4h	3,4-di-(OMe)C ₆ H ₃	O	18	88
4i	2-furyl	O	20	80
4j	5-methyl-2-furyl	O	20	95
4k	CH ₃	S	20	80
4l	4-(Cl)-C ₆ H ₄	S	20	82
4m	Ph-CH=CH	S	24	80

Reaction condition: **1** (a-m) (1 mmol), **2** (1 mmol), **3** (1.5 mmol), Si-Fe catalyst (10 mol%) in acetonitrile.

Aldehydes containing electron-donating or electron-withdrawing functional groups at different positions but it did not show any remarkable differences in the yields of product and reaction time. It was observed that the reaction of aromatic aldehydes with urea is very fast as compared to thiourea. The role of Si-Fe catalyst has been proposed to activate the aldehyde by binding the oxygen atom of aldehyde with transition metal Fe. Along with this we recovered the catalyst and reused for further reactions.

III. EXPERIMENTAL

General procedure for the synthesis of 3,4-dihydropyrimidinones: A solution of aldehyde (1.0 mmol), ethyl acetoacetate (156 mg, 1.2 mmol) and

urea (72 mg, 1.2 mmol) in acetonitrile (6 ml) was heated under reflux conditions in the presence of Si-Fe catalyst (10% w/w) for 16-24h. The progress of the reaction was monitored by TLC. The reaction mixture was then poured on crushed ice and the solid product obtained was filtered and washed with ice-cold water. To recover the catalyst from the product, the mixture was treated with hot ethanol and filtered. The residue, being the catalyst, was dried and reused for the next run without noticeable effect on the product yield. The filtrate on concentration afforded the product, which was found to be sufficiently pure. The products obtained were characterized by spectral (NMR and IR) data and by comparison with those of authentic samples.

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (Entry 4a): White solid; **MP:** 206-208°C; **IR** (neat) ν_{\max} : 3327, 3214, 1695, 1663 cm^{-1} ; **¹H NMR** (CDCl₃, 400 MHz): δ 1.08 (t, $J = 7.2$ Hz, 3H), 2.33 (s, 3H), 3.92 (q, $J = 7.2$ Hz, 2H), 5.22 (d, $J = 2.8$ Hz, 1H), 7.20-7.43 (m, 5H), 7.90 (s, 1H), 9.50 (s, 1H).

5-Ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (Entry 4e): White solid; **MP:** 210-212°C; **IR** (neat) ν_{\max} : 3233, 1743, 1630 cm^{-1} ; **¹H NMR** (CDCl₃, 400 MHz): δ 1.16 (t, $J = 7.2$ Hz, 3H), 2.34 (s, 3H), 4.06 (q, $J = 7.2$ Hz, 2H), 5.46 (d, $J = 2.8$ Hz, 1H), 6.51 (s, 1H), 7.49 (d, $J = 8.8$ Hz, 2H), 8.13 (d, $J = 8.8$ Hz, 2H), 8.39 (s, 1H).

5-Ethoxycarbonyl-6-methyl-4-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (Entry 4f): White solid; **MP:** 214-216°C; **IR** (neat) ν_{\max} : 3227, 1719, 1615 cm^{-1} ; **¹H NMR** (CDCl₃, 400 MHz): δ 1.20 (t, $J = 7.2$ Hz, 3H), 2.37 (s, 3H), 4.11 (q, $J = 7.2$ Hz, 2H), 5.40 (d, $J = 2.8$ Hz, 1H), 5.79 (s, 1H), 7.23-7.232 (m, 4H), 7.98 (s, 1H).

IV. CONCLUSION

We disclose here a simple, clean, atom-efficient, synthesis of dihydropyrimidinones using Si-Fe as catalysts. A simple experimental procedure, relatively fast reaction rates and excellent yields are the key advantages of our protocol. Most significantly, efficiency, and cost-effectiveness will make this procedure useful to academia as well as industry.

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VI. REFERENCES

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