

Ferric chloride/tetraethyl orthosilicate as an efficient system for synthesis of dihydropyrimidinones by Biginelli reaction

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Abstract—An efficient method for the Biginelli reaction of aldehydes, acetoacetate esters and urea employing tetraethyl orthosilicate in the presence of ferric chloride is described. These improved reaction conditions allow the preparation of a wide variety of substituted dihydropyrimidinones (including sterically encumbered ones) in high yields and purity under mild reaction conditions.
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1. Introduction

The Biginelli reaction¹ is a well-known, simple and straightforward procedure for the synthesis of dihydropyrimidinones by the three-component condensation of aliphatic or aromatic aldehyde, acetoacetate ester and urea. Since dihydropyrimidinones exhibit significant biological activity (e.g. as calcium channel blockers), their synthesis has been the focus of much interest from organic and medicinal chemists.² In its original version, the reaction is conducted in boiling ethanol in the presence of catalytic amounts of concentrated aqueous hydrochloric acid. This simple procedure has been effective in a number of the Biginelli reactions with simple unsubstituted, or *para*- and *meta*-substituted aldehydes and acetoacetate esters.^{3–9} However, in cases of significant steric hindrance in both counterparts the reaction yields drop drastically. In order to improve the yield of dihydropyrimidinones, a few other multistep approaches using aldehyde¹⁰ or acetoacetate¹¹ equivalents in modified Biginelli reactions have been developed. Nevertheless, the original Biginelli reaction offers the most simple, cost-effective and reasonable access to these important compounds.

During the last decade, several efficient methods based on metal-catalysed Biginelli reaction have been reported. Among the simple metal (and ammonium) salts with nucleophilic anions, e.g. LiBr,¹² NH₄Cl,¹³ NiCl₂·6H₂O,¹⁴ FeCl₃·6H₂O,¹⁴ CuCl₂·2H₂O,¹⁵ CeCl₃·7H₂O,¹⁶ Mn(OAc)₃·2H₂O,¹⁷ ZrCl₄,¹⁸ InCl₃,¹⁹ InBr₃,²⁰ ZnCl₂,²¹

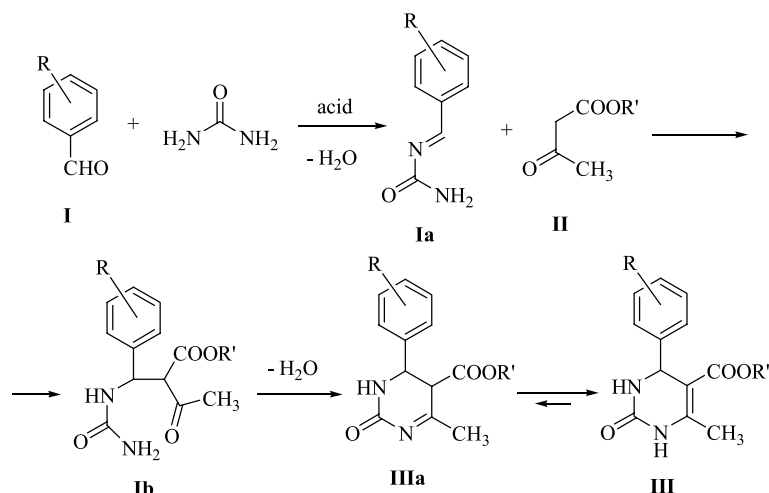
ZnI₂,²² CdCl₂,²³ BiCl₃²⁴ are active catalysts. The catalytic effect of metal cations is even more pronounced with methods based on metal salts with non-nucleophilic anions such as LiClO₄,²⁵ CuSO₄·5H₂O,¹⁵ Zn(OTf)₂,²⁶ Cu(OTf)₂,²⁷ Al(HSO₄)₃,²⁸ BiONO₃,²⁹ or various lanthanide triflates, Ln(OTf)₃ (Ln = Yb, Sc, La).^{30–32} The most efficient catalysts are bismuth triflate^{33,34} and trimethylsilyl triflate,³⁵ which allow the preparation of dihydropyrimidinones in good to high yields at room temperature. Another effective Biginelli reaction conditions employing stoichiometric reagents are BF₃·Et₂O and catalytic AcOH/CuCl in refluxing THF,³⁶ (CH₃)₃SiCl (TMSCl),³⁷ TMSCl/NaI,³⁸ or TMSCl/DMFA.³⁹ Additionally, the Biginelli reaction can be strongly accelerated by various ionic liquids in catalytic amounts, e.g. 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (BMImBF₄).⁴⁰ Finally the reaction can be performed by simple heating a neat mixture of aldehyde, acetoacetate and urea (in slight excess) at 100–105 °C under solventless conditions for a few hours with fair yields.⁴¹

Although many of the above mentioned methods give pure dihydropyrimidinone in good to excellent yields, in almost all cases the model compounds were selected from simple acetoacetate esters, either methyl or ethyl acetoacetate, and, mainly, *meta*- and *para*-substituted aromatic aldehydes with no significant steric demands. As a consequence, many of these methods do not work with sterically encumbered Biginelli counterparts.

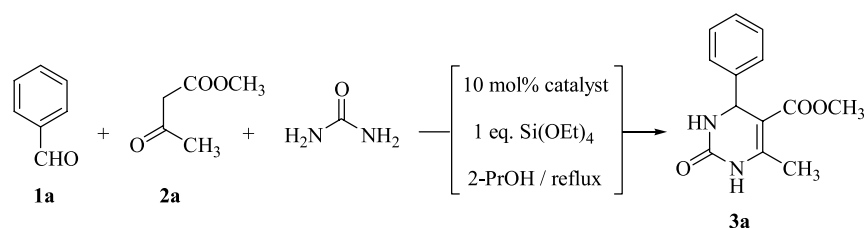
In contrast to simple catalytic methods, those employing suitable dehydrating agents have proved more effective, even in the cases of more complicated dihydropyrimidinones. Thus, Kappe and coworkers⁴² described a simple, effective and general method for Biginelli reaction based on

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Scheme 1.



Scheme 2.

ethyl polyphosphate (PPE) mediated reaction under quite mild reaction conditions (refluxing THF). Moreover, it has been found that the procedure can be further speeded-up using microwave heating.⁴³ Except the work from Kappe's group, not much attention has been paid to the synthetic methods applicable to all kinds of dihydropyrimidinones, including the sterically hindered ones.

We decided to study the Biginelli reaction based on tetraethyl orthosilicate ($\text{Si}(\text{OEt})_4$) in the presence of a suitable acid catalyst. $\text{Si}(\text{OEt})_4$ is an extremely efficient reagent in the synthesis of sterically encumbered Schiff's bases.⁴⁴ Since the generally accepted Biginelli reaction mechanism^{45–47} (Scheme 1) involves the formation of C=N bond from the parent aldehyde (**I**) and urea followed by (protic or Lewis) acid-catalysed addition of acetoacetate ester (**II**) to the protonated aryl(or alkyl)idene-urea (**Ia**) and cyclodehydration (via **Ib**) yielding dihydropyrimidinones (**III**), $\text{Si}(\text{OEt})_4$ might promote the reaction by accelerating the formation C=N bond (rate-determining step).

The same effect was successfully employed in the synthesis of 1,4-dihydropyridines, where $\text{Si}(\text{OEt})_4$ dramatically accelerates the acid-catalysed Hantzsch condensation of aldehyde, acetoacetate ester and ammonium acetate furnishing very pure 1,4-dihydropyridines in excellent yields.⁴⁸

2. Results and discussion

First, we examined the effect of various Lewis acids and 10 mol % PhSO_3H on the model reaction of benzaldehyde

(**1a**, 1 equiv), methyl acetoacetate (**2a**, 1.05 equiv), and urea (1.2 equiv) in the presence of $\text{Si}(\text{OEt})_4$ (1 equiv) affording 5-methoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (**3a**) in various yields (Scheme 2). Since the model reaction catalysed by PhSO_3H performed in refluxing acetonitrile (80 °C) or THF (65 °C) gave significantly lower yields than in isopropanol, all other reactions in this study were conducted in the latter reaction solvent. The results are presented in Table 1.

Table 1. Catalyst effect in the model Biginelli reaction (Scheme 2)

Entry	Catalyst (10 mol%)	Time (h) ^a	Yield (%) ^b
1	–	24	8
2 ^c	37% HCl aq.	5	47
3	PhSO_3H	4	59 (51, ^d 43 ^e)
4	NiCl_2	20	72
5	CeCl_3	20	65
6	ZnCl_2	20	52
7	AlCl_3	20	64
8	CuCl_2	4	71
9	$\text{Cu}(\text{OTf})_2$	4	75
10	$\text{Fe}(\text{OAc})_2$	24	41
11	FeCl_3 ^f	2.5	88
12	FeCl_3 ^f	4	94

^a The reactions were monitored by TLC until the disappearance of starting methyl acetoacetate (**2a**).

^b Yields of isolated and recrystallised product (from 96% EtOH).

^c This reaction was carried out in refluxing 96% EtOH, representing the classical Biginelli conditions.

^d In refluxing MeCN.

^e In refluxing THF.

^f Methyl acetoacetate (**2a**) was added dropwise to the reaction mixture at reflux temperature during 2 h, plus 2 h additional heating.

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