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$Cu(ClO_4)_2 \cdot 6H_2O$ AS AN EFFICIENT CATALYST FOR THE SYNTHESIS OF 3,4-DIHYDROPYRIMIDIN-2(1*H*)-ONES UNDER SOLVENT-FREE CONDITIONS

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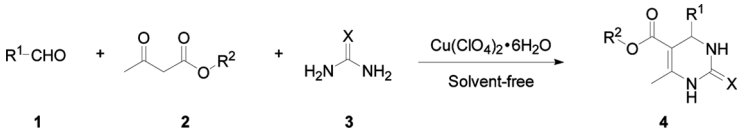
GRAPHICAL ABSTRACT



Abstract *$Cu(ClO_4) \cdot 6H_2O$ efficiently catalyzes the three-component Biginelli reaction of aldehyde, β-dicarbonyl compounds, and urea or thiourea under solvent-free conditions to afford the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones in excellent yields.*

Keywords β-Amino carbonyl compounds; aldehydes; Biginelli reaction; $Cu(ClO_4) \cdot 6H_2O$

INTRODUCTION

Dihydropyrimidinones and their derivatives are an important class of compounds because of their therapeutic and pharmacological properties,[1] such as antibacterial, antiviral, antitumor, and anti-inflammatory activities. In recent years, many members of this family have served as integral backbones of several calcium channel blockers, antihypertensive agents, α-1a-antagonists, and neuropeptide Y(NPY) antagonists.[2] Furthermore, several isolated marine alkaloids[3] with interesting biological activities have also been found to contain the dihydropyrimidinone-5-carboxylate core. Among these, most notable are the batzelladine alkaloids, which have been found to be potent HIV gp-120-CD4 inhibitors.[4] Therefore, the synthesis of this heterocyclic nucleus has gained a great importance in organic synthesis.

The Biginelli reaction is a simple one-pot cyclocondensation of β-dicarbonyl compounds with aldehydes and urea or thiourea in the presence of a catalytic

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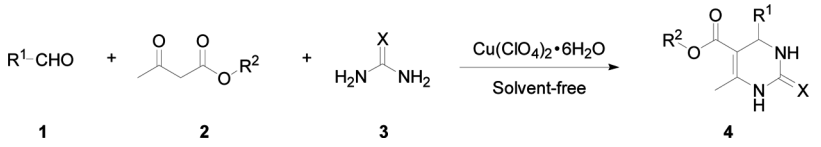


Scheme 1. Biginelli reaction catalyzed by $Cu(ClO_4)\cdot 6H_2O$.

amount of HCl.[1a] However, yields of 3,4-dihydropyrimidin-2(1*H*)-ones obtained by the Biginelli reaction are poor in the case of substituted aromatic and aliphatic aldehydes.[1a] To improve the yields of the Biginelli reaction, the use of a number of Lewis acid catalysts, such as $BF_3 \cdot OEt_2$,[5] $FeCl_3$,[6] $ZrCl_4$,[7] $BiCl_3$,[8] $LaCl_3$,[9] $InCl_3$,[10] $Cu(OTf)_2$,[11] $Sc(OTf)_2$,[12] $Bi(OTf)_3$,[13] $CeCl_3$,[14] and ionic liquid,[15] have been reported. Additionally, the Biginelli reaction can strongly be accelerated by various procedures including heteropoly acid,[16] ultrasound irradiation,[17] and microware irradiation.[18]

Although numerous modified methods have been reported, many of these methods have drawbacks, such as harsh reaction conditions, poor yields, cumbersome workup procedures, and long reaction time. Furthermore, many of these procedures require strongly acidic conditions. With increasing environmental consciousness in chemical research and industry, the challenge for a sustainable environment calls for clean procedures that avoid using harmful organic solvents or do not need solvents at all. In this article, we report a mild, efficient, and solvent-free procedure for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones by the condensation of β-dicarbonyl compounds with aldehydes and urea or thiourea in the presence of a catalytic amount of $Cu(ClO_4)_2 \cdot 6H_2O$ (1 mol%) under stirring at 60 °C in solvent-free conditions (Scheme 1).

RESULTS AND DISCUSSION

Initially, we have studied the Biginelli one-pot condensation reaction of benzaldehyde (2 mmol), ethyl acetoacetate (2 mmol), and urea (3 mmol) using 1 mol% $Cu(ClO_4)_2 \cdot 6H_2O$ in EtOH as solvent at 60 °C for 240 min. After completion of the condensation, thin-layer chromatography monitored by (TLC), the reaction mixture was poured into cold water and stirred for 5 min, and the corresponding product was obtained by simple filtration in good yield (91%).

To improve the product yield and to optimize the reaction conditions, a series of reaction conditions using $Cu(ClO_4)_2 \cdot 6H_2O$ as a catalyst were examined when the substrates were benzaldehyde, ethyl acetoacetate, and urea. The results are summarized in Table 1. To determine the most appropriate solvent, the reaction was examined using EtOH, MeOH, MeCN, tetrahydrofuran (THF), dichloromethane (DCM), and H_2O. EtOH and MeCN were effective. We also found that the Biginelli reaction could be carried out under solvent-free condition in excellent yield (93%). We subsequently changed the amount of $Cu(ClO_4)_2 \cdot 6H_2O$ from 0 mol% to 5 mol% under solvent-free conditions, and 1 mol% performed significantly better (93% yield). The results indicated that 1 mol% of $Cu(ClO_4)_2 \cdot 6H_2O$ is sufficient, and excessive amounts of catalyst do not increase the yields significantly.

Table 1. $Cu(ClO_4)_2 \cdot 6H_2O$-catalyzed condensation of benzaldehyde, ethyl acetoacetate, and urea[a]

Entry	Catalyst (mol%)	Solvent	Time (min)	Yield of **4a** (%)[b]
1	1	EtOH	240	91
2	1	MeOH	240	88
3	1	MeCN	240	91
4	1	THF	240	84
5	1	DCM	240	85
6	1	H_2O	360	20
7	0	None	240	0
8	0.5	None	40	80
9	1	None	30	93
10	3	None	20	93
11	5	None	20	94

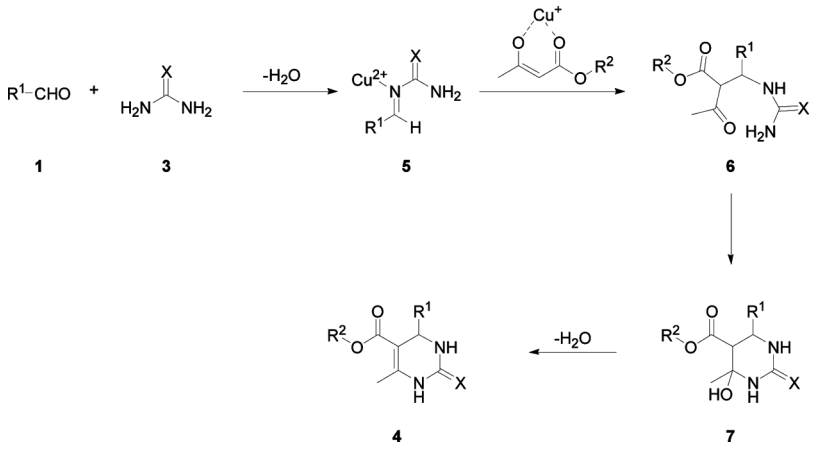
[a]The reactions were carried out in the presence of benzaldehyde (2 mmol), ethyl acetoacetate (2 mmol), and urea (3 mmol) at 60 °C.
[b]Isolated yield after recrystallization.

We selected the optimized reaction conditions to examine the application of the catalyst. A series of aldehydes were selected to undergo the condensation in the presence of a catalytic amount of $Cu(ClO_4)_2 \cdot 6H_2O$ (1 mol%) at 60 °C under solvent-free conditions (Table 2). We found that this one-step procedure worked well

Table 2. $Cu(ClO_4)_2 \cdot 6H_2O$-catalyzed dihydropyrimidinones under solvent-free conditions[a]

Entry	R^1	R^2	X	Time (min)	Yield of **4** (%)[b]	Mp (°C) found	Mp (°C) reported
4a	C_6H_5	Et	O	30	93	205–208	206–208[12]
4b	4-$CH_3C_6H_4$	Et	O	30	93	204–205	205–206[12]
4c	4-$CH_3OC_6H_4$	Et	O	30	95	199–201	200–201[11]
4d	4-$(CH_3)_2NC_6H_4$	Et	O	60	90	254–256	253–254[12]
4e	4-OHC_6H_4	Et	O	30	88	237–239	237–238[12]
4f	3-$NO_2C_6H_4$	Et	O	40	87	233–234	230–232[12]
4g	2,4-$Cl_2C_6H_3$	Et	O	60	91	252–254	251–253[19]
4h	2-Furyl	Et	O	45	83	208–210	208–210[12]
4i	PhCH=CH	Et	O	30	92	233–234	231–232[18c]
4j	CH_3CH_2	Et	O	60	88	180–182	179–181[20]
4k	$CH_3CH_2CH_2$	Et	O	20	86	155–157	154–157[21]
4l	$(CH_3)_2CH$	Et	O	10	90	196–198	195–196[22]
4m	C_6H_5	Me	O	30	95	214–216	212–213[12]
4n	4-$CH_3C_6H_4$	Me	O	40	93	200–202	200–203[23]
4o	4-$CH_3OC_6H_4$	Me	O	40	93	194–195	190–192[21]
4p	4-OHC_6H_4	Me	O	30	87	222–224	226–228[21]
4q	3-$NO_2C_6H_4$	Me	O	30	89	271–274	273–275[12]
4r	C_6H_5	Et	S	120	84	205–207	207–208[12]
4s	4-$CH_3C_6H_4$	Et	S	120	86	212–214	214–215[12]
4t	4-$CH_3OC_6H_4$	Et	S	120	85	153–155	150–152[20]
4u	3-$NO_2C_6H_4$	Et	S	120	86	207–209	206–207[12]

[a]The reactions were carried out in the presence of aldehyde (2 mmol), β-diketoeaster (2 mmol), and urea or thiourea (3 mmol) at 60 °C.
[b]Isolated yield after recrystallization.



Scheme 2. A possible mechanism for Biginelli reaction catalyzed by $Cu(ClO_4)\cdot 6H_2O$.

for a variety of aldehydes. The results are shown in Table 2. Both aromatic and aliphatic aldehydes could react efficiently to give the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones in good yields. Aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents afforded good yields. Similarly, the α,β-unsaturated aldehyde also gave the product (entry **4i**) in 92% yield. Furthermore, the usefulness of this methodology has also been extended successfully with thiourea in a similar manner to provide the corresponding 3,4-dihydropyrimidin-2(1*H*)-thiones in good yields.

We propose a mechanism of the Cu(II)-catalyzed reaction as shown in Scheme 2. The aldehyde reacts with urea to form an acyl imine intermediate **5**, which is activated by Cu(II). Subsequent addition of the β-dicarbonyl compound, followed by cyclization and dehydration, afforded the dihydropyrimidin-2(1*H*)-ones **4**.[9,11,12]

In conclusion, we have described a simple, efficient, and practical method for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones by using $Cu(ClO_4)_2 \cdot 6H_2O$ under solvent-free conditions. A simple workup procedure, mild reaction conditions, short reaction times, environmentally friendly procedure, and very good yields make our methodology a valid contribution to the existing processes in the field of dihydropyrimidin-2(1*H*)-one derivative synthesis.

EXPERIMENTAL

All reagents were commercially available and used without further purification. The melting points were recorded on Digital melting-point apparatus WRS-1B and are uncorrected. ^{1}H NMR spectra were recorded on Bruker WP-500SY (500 MHz) instrument using tetramethylsilane (TMS) as an internal standard.

General Procedure for the Preparation of 3,4-Dihydropyrimidiones 4

A mixture of aldehyde (2 mmol), β-dicarbonyl compound (2 mmol), urea or thiourea (3 mmol), and $Cu(ClO_4)_2 \cdot 6H_2O$ (0.02 mmol, 1 mol%) was heated at 60 °C

under stirring for the appropriate time (Table 2). After completion of the reaction as indicated by TLC, the reaction mixture was poured into cold water and stirred for 5 min. The solid was filtered, and recrystallized from EtOH or *i*-PrOH to afford the pure product.

Selected 1H NMR Data

Compound 4a. ^{1}H NMR (500 MHz, $CDCl_3$) 7.74 (s, 1H, NH), 7.25–7.35 (m, 5H, ArH), 5.58 (s, 1H, NH), 5.41 [s, 1H, CH), 4.07–4.08 (m, 2H, CH_2], 2.35 (s, 3H, CH_3), 1.16 (t, 3H, $J = 6.98$ Hz, CH_3).

Compound 4c. ^{1}H NMR (500 MHz, $CDCl_3$) 7.63 (s, 1H, NH), 7.25 (d, 2H, $J = 8.65$ Hz, ArH), 6.84 (d, 2H, $J = 8.65$ Hz, ArH), 5.52 (s, 1H, NH), 5.35 (s, 1H, CH), 4.05–4.10 (m, 2H, CH_2), 3.79 (s, 3H, CH_3O), 2.34 (s, 3H, CH_3), 1.16 (t, 3H, $J = 7.11$ Hz, CH_3).

Compound 4d. ^{1}H NMR (500 MHz, $CDCl_3$) 7.63 (s, 1H, NH), 7.18 (d, 2H, $J = 8.67$ Hz, ArH), 6.65 (d, 2H, $J = 8.67$ Hz, ArH), 5.45 (s, 1H, NH), 5.31 (s, 1H, CH), 4.07 (q, 2H, $J = 7.12$ Hz, CH_2), 2.92 [s, 6H, $N(CH_3)_2$], 2.33 (s, 3H, CH_3), 1.19 (t, 3H, $J = 7.12$ Hz, CH_3).

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