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Efficient, Green, Solvent-Free Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones via Biginelli Reaction Catalyzed by $Cu(NO_3)_2 \cdot 3H_2O$

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EFFICIENT, GREEN, SOLVENT-FREE SYNTHESIS OF 3,4-DIHYDROPYRIMIDIN-2(1H)-ONES VIA BIGINELLI REACTION CATALYZED BY $Cu(NO_3)_2 \cdot 3H_2O$

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The synthesis of 3,4-dihydropyrimidin-2-(1H)-ones derivatives via a three-component Biginelli reaction using copper nitrate as a catalyst under solventless conditions is reported, providing a green, rapid, efficient, and convenient method for the preparation of Biginelli compounds in good yields.

Keywords: Biginelli reaction; copper nitrate; 3,4-dihydropyrimidin-2(1H)-ones

INTRODUCTION

3,4-Dihydropyrimidin-2-(1H)-ones (DHPMs) have attracted considerable interest in recent years because of their important pharmacological properties and use as calcium channel blockers (**1**),[1a] antihypertensive agents (**2**),[1a] α_{1a}-antagonists,[1b] mitotic kinesin Eg5 inhibitors (**3**),[1c] melanin concentrating hormone receptor antagonists (**4**),[1d] and neuropeptide antagonists (Fig. 1). Moreover, some alkaloids containing the dihydropyrimidine core unit, isolated from marine sources, also show interesting biological properties. Most noteworthy among these are the batzelladine alkaloids (**5**) (Fig. 1), known to be potent HIV gp-120-CD4 inhibitors.[2]

The Biginelli reaction,[3] one of the most useful multicomponent reactions, is a one-pot cyclocondensation reaction of β-ketone ester with aldehydes and urea in the presence of acid, and it provides the most simple and straightforward route to DHPMs. One major drawback of this Biginelli reaction is the poor to moderate yields (20–50%). Recently, because of the simplicity of the synthesis of DHPMs, the Biginelli reaction has received renewed interest. To enhance the efficiency of the Biginelli reaction, various catalysts and reaction conditions have been studied, and many improved procedures catalyzed by different Lewis and protic acids such as $CeCl_3$,[4] $Cu(OTf)_2$,[5a] $Cu(BF_4)_2$,[5b] $Mg(ClO_4)_2$,[6a] heteropoly acids,[6b] $Y(NO_3)_3$,[6c] Ziegler–Natta,[6d] $PhB(OH)_2$,[7a] propane phosphonic acid anhydride,[7b]

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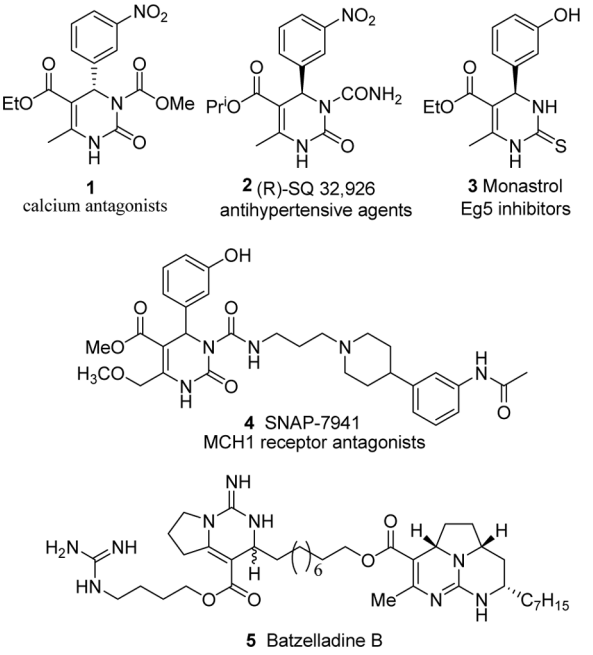


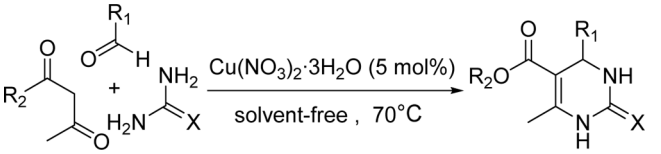
Figure 1. Dihydropyrimidine antagonists.

triphenylphosphine,[7c] hydrazine,[7d] $SiCl_4$,[8] ionic liquid,[9] graphite–$LaCl_3$,[10] and polyethylene glycol (PEG)[11] have been reported.

However, some of these procedures involve drawbacks, such as the need for strong acids, anhydrous conditions, toxic organic solvents, costly catalysts, high temperatures, and complex operation and create environmental disposal problems. Therefore, the search for a milder and environmentally acceptable catalytic method for performing the Biginelli reaction has attracted much attention. Here, we report a general and practical route for the Biginelli cyclocondensation reaction using copper nitrate as a catalyst under solventless conditions at 70 °C. As far as we know, there was no report for the synthesis of DHPMs catalyzed by $Cu(NO_3)_2 \cdot 3H_2O$ (Scheme 1).

RESULTS AND DISCUSSION

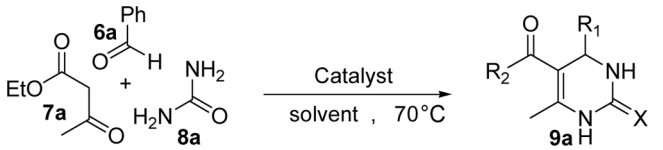
To evaluate the effect of the catalyst under different reaction conditions, the reaction of benzaldehyde, ethyl acetoacetate, and urea was selected as a model



Scheme 1. Biginelli reaction catalyzed by $Cu(NO_3)_2 \cdot 3H_2O$.

reaction, and the results are summarized in Table 1. Initially, the effects of different catalysts on the reaction system were studied without solvents, and the results showed that $Cu(NO_3)_2 \cdot 3H_2O$ among all metal nitrates examined was the optimal catalyst for this condensation (entries 1–8). Second, we examined different reaction conditions in traditional organic solvents, water, and solvent-free conditions at 70 °C. Excellent yields of the product **9a** were observed with EtOH (yield 97%), tetrahydrofuran (THF; 96%), CH_3CN (95%), no solvent (95%), and H_2O (88%) (entries 8, 12–15), and lower yield was observed in CH_2Cl_2 (60%) (entry 16). At the same time, we found that the temperature had little impact on the catalytic capacity of copper nitrate; the excellent yields of the product **9a** were observed in THF (93%) (entry 17) at room temperature. Considering the efficiency and environment, the solvent-free condition was selected for the reaction at 70 °C. Third, the effect of catalyst loading on the reaction efficiency was evaluated (entries 8–11). A similar result was obtained for the reaction catalyzed by 10 mol% of $Cu(NO_3)_2 \cdot 3H_2O$ as the reaction catalyzed by 5 mol% of $Cu(NO_3)_2 \cdot 3H_2O$. The yield of product **9a** was 91% even using 1 mol% $Cu(NO_3)_2 \cdot 3H_2O$ (entry 11). Finally, after completion of the reaction, 10 mL of water were added to the mixture and stirred for 10 min. The product **9a** was obtained by filtration and washed with water without recrystallization.

Table 1. Reaction of benzaldehyde, ethyl acetoacetate, and urea under different reaction conditions[a]



Entry	Solvent	Catalyst (mol%)	Time	Yield (%)[b]
1	None	$Ce(NO_3)_2 \cdot 6H_2O$ (10)	30 min	79
2	None	$Fe(NO_3)_2 \cdot 9H_2O$ (10)	30 min	75
3	None	$Ba(NO_3)_2$ (10)	30 min	25
4	None	$Mg(NO_3)_2 \cdot 6H_2O$ (10)	30 min	60
5	None	$Al(NO_3)_2 \cdot 9H_2O$ (10)	30 min	67
6	None	$Ca(NO_3)_2 \cdot 4H_2O$ (10)	30 min	46
7	None	$La(NO_3)_2 \cdot 6H_2O$ (10)	30 min	72
8	None	$Cu(NO_3)_2 \cdot 3H_2O$ (10)	30 min	95
9	None	$Cu(NO_3)_2 \cdot 3H_2O$ (5)	40 min	93
10	None	$Cu(NO_3)_2 \cdot 3H_2O$ (2)	4 h	91
11	None	$Cu(NO_3)_2 \cdot 3H_2O$ (1)	4 h	91
12	EtOH	$Cu(NO_3)_2 \cdot 3H_2O$ (10)	6 h	97
13	THF	$Cu(NO_3)_2 \cdot 3H_2O$ (10)	6 h	96
14	CH_3CN	$Cu(NO_3)_2 \cdot 3H_2O$ (10)	6 h	95
15	H_2O	$Cu(NO_3)_2 \cdot 3H_2O$ (10)	8 h	88
16	CH_2Cl_2	$Cu(NO_3)_2 \cdot 3H_2O$ (10)	6 h	60
17	THF	$Cu(NO_3)_2 \cdot 3H_2O$ (10)	24 h	93[c]

[a]Reaction conditions: benzaldehyde (3 mmol), ethyl acetoacetate (4.5 mmol), urea (6 mmol), and catalyst stirring in solvent (2 mL, entries 12–16) at 70 °C.

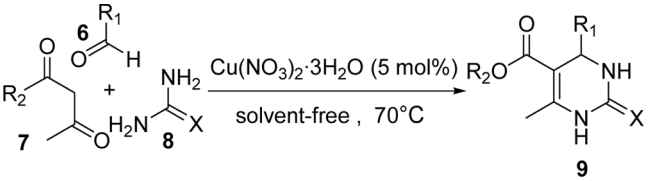
[b]Isolated yield.

[c]Room temperature.

To evaluate the generality of the procedure, a series of Biginelli compounds were synthesized under the optimized conditions as shown in Table 2. The original Biginelli products from ethyl acetoacetate were obtained in good yield under these reaction conditions (entries 1–8), and the products from acetylacetone were also obtained in good yield (entries 9–17). When thiourea was used as reactant, S-analogs of DHPMs could be easily obtained in excellent yields (entries 7, 10, and 12). More important, the different substituent groups of aromatic aldehydes, such as either electron-donating or electron-withdrawing substituents, had little impact on the yields of the products. Further, the reactivity of aliphatic aldehydes was examined. The Biginelli reaction of cyclohexanecarboxaldehyde catalyzed by copper nitrate without solvent at 70 °C for 25 min afforded **9h** (yield 78%) and **9q** (77%) (entries 8 and 17). Compared to the traditional methods, it has an advantage in yield.

In summary, this report describes a green, simple, and efficient one-pot procedure for the synthesis of Biginelli DHPMs using $Cu(NO_3)_2 \cdot 3H_2O$ as a catalyst under solvent-free conditions. This method offers several advantages such as mild reaction conditions, excellent yields, short reaction times, and ease of manipulation.

Table 2. Copper nitrate-catalyzed synthesis of different dihydropyrimidinones under solventless conditions[a]



Entry	Compound	R1	R2	X	Time	Yield (%)[b]
1	**9a**	C_6H_5	EtO	O	40 min	93
2	**9b**	4-CH_3O-C_6H_4	EtO	O	40 min	94
3	**9c**	4-CH_3-C_6H_4	EtO	O	30 min	93
4	**9d**	4-Cl-C_6H_4	EtO	O	50 min	95
5	**9e**	4-NO_2-C_6H_4	EtO	O	40 min[c]	96
6	**9f**	3-NO_2-C_6H_4	EtO	O	40 min	89
7	**9g**	4-CH_3O-C_6H_4	EtO	S	8 h[c]	87
8	**9h**	Cyclohexyl	EtO	O	25 min	78
9	**9i**	C_6H_5	Me	O	25 min	96
10	**9j**	C_6H_5	Me	S	2.5 h[c]	86
11	**9k**	4-CH_3O-C_6H_4	Me	O	60 min	96
12	**9l**	4-CH_3O-C_6H_4	Me	S	8 h	85
13	**9m**	4-CH_3-C_6H_4	Me	O	30 min	97
14	**9n**	4-Cl-C_6H_4	Me	O	30 min	94
15	**9o**	4-NO_2-C_6H_4	Me	O	30 min[c]	95
16	**9p**	3-NO_2-C_6H_4	Me	O	30 min	98
17	**9q**	Cyclohexyl	Me	O	25 min	77

[a]Reaction conditions: aldehyde (3 mmol), ethyl acetoacetate or acetylacetone (4.5 mmol), urea or thiourea (6 mmol), and $Cu(NO_3)_2 \cdot 3H_2O$ (5 mol%) stirring without a solvent at 70 °C.

[b]Isolated yield.

[c]90 °C.

Apart from water, no solvents were used in the procedure. It is noteworthy synthetic methodology for the preparation of DHPMs.

EXPERIMENTAL

General Procedure for Synthesis of DHPMs

A mixture of aldehyde (3 mmol), ethyl acetoacetate or acetylacetone (4.5 mmol), urea or thiourea (6 mmol), and $Cu(NO_3)_2 \cdot 3H_2O$ (0.15 mmol) was heated at 70 °C under stirring for the appropriate time (Table 2). Then water was added, and the mixture was stirred for 10 min. The solid was filtered and washed with cold water but not recrystallized to afford the pure product (**9**).

^{1}H NMR Spectral and Melting-Point Data for All the Products

Compound 9a. Mp 202–203 °C. ^{1}H NMR (DMSO-d_6): δ = 9.18 (s, 1H), 7.73 (s, 1H), 7.27 (m, 5H), 5.14 (d, J = 3.2 Hz, 1H), 3.98 (q, J = 7 Hz, 2H), 2.25 (s, 3H), 1.09 (t, J = 7 Hz, 3H).

Compound 9b. Mp 199–201 °C. ^{1}H NMR ($CDCl_3$): δ = 8.39 (s, 1H), 5.92 (s, 1H), 7.24 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 5.36 (s, 1H), 3.95 (q, J = 6.8 Hz, 2H), 3.79 (s, 3H), 2.34 (s, 3H), 1.18 (t, J = 6.8 Hz, 3H).

Compound 9c. Mp 214–216 °C. ^{1}H NMR ($CDCl_3$): δ = 7.39 (s, 1H), 7.22 (d, J = 7.6 Hz, 2H), 7.13 (d, J = 7.6 Hz, 2H), 5.47 (s, 1H), 5.38 (s, 1H), 4.09 (q, J = 7.0 Hz, 2H), 2.34 (s, 6H), 1.19 (t, J = 7.0 Hz, 3H).

Compound 9d. Mp 213–215 °C. ^{1}H NMR ($CDCl_3$): δ = 7.84 (s, 1H), 7.28 (m, 4H), 5.73 (s, 1H), 5.40 (s, 1H), 4.10 (q, J = 6.8 Hz, 2H), 2.36 (s, 3H), 1.19 (t, J = 6.8 Hz, 3H).

Compound 9e. Mp 206–208 °C. ^{1}H NMR (DMSO-d_6): δ = 9.37 (s, 1H), 8.23 (d, J = 8 Hz, 2H), 7.91 (s, 1H), 7.52 (d, J = 8 Hz, 2H), 5.29 (s, 1H), 4.00 (q, J = 6.8 Hz, 2H), 2.28 (s, 3H), 1.11 (t, J = 6.8 Hz, 3H).

Compound 9f. Mp 230–231 °C. ^{1}H NMR (DMSO-d_6): δ = 9.36 (s, 1H), 8.07–8.14 (m, 2H), 7.89 (s, 1H), 7.68 (m, 2H), 5.29 (d, J = 2 Hz, 1H), 4.00 (q, J = 6.8 Hz, 2H), 2.27 (s, 3H), 1.09 (t, J = 6.8 Hz, 3H).

Compound 9g. Mp 153–154 °C. ^{1}H NMR (DMSO-d_6): δ = 10.27 (s, 1H), 9.58 (s, 1H), 7.12 (d, J = 7.2 Hz, 2H), 6.90 (d, J = 7.2 Hz, 2H), 5.11 (s, 1H), 4.01 (q, J = 6.8 Hz, 2H), 3.72 (s, 3H), 2.28 (s, 3H), 1.10 (t, J = 6.8 Hz, 3H).

Compound 9h. Mp 232–234 °C. ^{1}H NMR (DMSO-d_6): δ = 8.88 (s, 1H), 7.29 (s, 1H), 4.05 (q, J = 7.2 Hz, 2H), 3.92 (t, J = 3.6 Hz, 1H), 2.16 (s, 3H), 1.68 (m, 2H), 1.58 (m, 2H), 1.39–1.27 (m, 3H), 1.18 (t, J = 7.2 Hz, 3H), 1.13–1.05 (m, 4H).

Compound 9i. Mp 236–238 °C. ^{1}HNMR (DMSO-d_6): δ = 9.17 (s, 1H), 7.81 (s, 1H), 7.22–7.34 (m, 5H), 5.26 (d, J = 3.6 Hz, 1H), 2.29 (s, 3H), 2.10 (s, 3H).

Compound 9j. Mp 186–188 °C. ^{1}HNMR (DMSO-d_6): δ = 10.28 (s, 1H), 9.75 (s 1H), 7.22–7.34 (m, 5H), 5.30 (d, J = 4 Hz, 1H), 2.33 (s, 3H), 2.15 (s, 3H).

Compound 9k. Mp 172–174 °C. ^{1}HNMR (DMSO-d_6): δ = 9.13 (s, 1H), 7.75 (s 1H), 7.15 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 5.19 (d, J = 3.2 Hz, 1H), 3.72 (s, 3H), 2.27 (s, 3H), 2.07 (s, 3H).

Compound 9l. Mp 186 °C. ^{1}H NMR ($CDCl_3$): δ = 7.56 (s, 1H), 7.19 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 1.6 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 5.40 (d, J = 1.6 Hz, 1H), 3.79 (s, 3H), 2.35 (s, 3H), 2.12 (s, 3H).

Compound 9m. Mp 208–210 °C. ^{1}H NMR (DMSO-d_6): δ = 9.16 (s, 1H), 7.79 (s, 1H), 7.13 (s, 4H), 5.21 (d, J = 3.2 Hz, 2H), 2.28 (s, 3H), 2.26 (s, 3H), 2.08 (s, 3H).

Compound 9n. Mp 210–212 °C. ^{1}H NMR (DMSO-d_6): δ = 9.24 (s, 1H), 7.87 (s, 1H), 7.40 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 5.25 (d, J = 3.2 Hz, 1H), 2.29 (s, 3H), 2.13 (s, 3H).

Compound 9o. Mp 268–270 °C. ^{1}HNMR (DMSO-d_6): δ = 9.33 (s, 1H), 8.20 (d, J = 8.8 Hz, 2H), 7.98 (s, 1H), 7.50 (d, J = 8.8 Hz, 2H), 5.39 (d, J = 3.6 Hz, 1H), 2.31 (s, 3H), 2.18 (s, 3H).

Compound 9p. Mp 278–280 °C. ^{1}HNMR (DMSO-d_6): δ = 9.37 (s, 1H), 8.10–8.13 (m, 2H), 8.02 (s, 1H), 7.61–7.68 (m, 2H), 5.40 (d, J = 3.2 Hz, 1H), 2.32 (s, 3H), 2.19 (s, 3H).

Compound 9q. Mp 189–191 °C. ^{1}H NMR (DMSO-d_6): δ = 8.85 (s, 1H), 7.32 (s, 1H), 4.00 (t, J = 3.6 Hz, 1H), 2.20 (s, 3H), 2.17 (s, 3H), 1.66–1.70 (m, 4H), 1.56–1.60 (m, 3H), 1.05–1.14 (m, 4H).

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