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## Cu(OTf)<sub>2</sub>: a reusable catalyst for high-yield synthesis of 3,4-dihydropyrimidin-2(1H)-ones

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Abstract—Copper(II) triflate catalyzes efficiently the three-component condensation reaction of an aldehyde,  $\beta$ -ketoester and urea in acetonitrile to afford the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones in high yields. The catalyst exhibited remarkable reusable activity. © 2003 Elsevier Science Ltd. All rights reserved.

Biginelli reactions are simple one-pot but low-yielding condensations of  $\beta$ -dicarbonyl compounds with aldehydes and urea or thiourea in the presence of catalytic amount of acid to produce 3,4-dihydropyrimidin-2-(1H)-ones.<sup>1</sup> In recent years, interest in this reaction has increased rapidly and several modified procedures aimed at improving the efficiency of the Biginelli dihydropyrimidine synthesis have been reported. For example, modifications and improvements using Lewis acids such as BF<sub>3</sub>·OEt<sub>2</sub>, FeCl<sub>3</sub>, LaCl<sub>3</sub>, La(OTf)<sub>3</sub>, Yb(OTf)<sub>3</sub>, InX<sub>3</sub> (X=Cl, Br), ZrCl<sub>4</sub>, BiCl<sub>3</sub>, Mn(OAc)<sub>3</sub>, LiClO<sub>4</sub>, clays, etc have been reported.<sup>2</sup> However, some of these procedures involve difficulties such as the use of stoichiometric amounts of catalysts, high temperatures, the use of metal halides as catalysts, the separation of the product from the catalyst, etc. Moreover, the recovery and reuse of catalysts in any such process offers advantages in terms of a clean and environmentally benign process. We wish to report here a simple but effective procedure for Biginelli's three-component cyclocondensation producing high yields of 3,4-dihydropyrimidin-2(1*H*)-ones **2** by employing  $Cu(OTf)_2^3$  as a reusable catalyst (Scheme 1).

The results of optimization experiments for the threecomponent Biginelli condensation involving benzaldehyde, urea and ethyl acetoacetate with copper salts as catalysts are presented in Table 1. It is remarkable to note that the condensation proceeded with a low catalyst concentration [0.5 mol% of Cu(OTf)<sub>2</sub>] at ambient conditions and gave 3,4-dihydropyrimidin-2(1H)-one 2a in high yields. Solvents such as CH<sub>3</sub>CN, THF and EtOH proved to be effective. After the reaction was complete as monitored by TLC, the product 2a was isolated by simple filtration. When the filtered solution containing the Cu(OTf)<sub>2</sub> was further treated with the reactants, only a slight decrease in the yield (from 95 to 80% after the fifth time) of the 3,4-dihydropyrimidin-2(1H)-one 2a was observed (Table 1). In another experiment, when the filtered solution containing the catalyst was used after 6 months of storage, it was observed that the catalyst was quite active (no appreciable change in the yield of the product), demonstrating that  $Cu(OTf)_2$  is stable and does not undergo any deterioration. This study demonstrates that Cu(OTf)<sub>2</sub> can be effectively used as a reusable catalyst for Biginelli-type condensations. Also the reaction can be



Scheme 1. Reagents and conditions: (i) Cu(OTf)<sub>2</sub> (0.5 mol), CH<sub>3</sub>CN, 25°C, 12 h.

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Table 1. Cu-catalyzed condensation of benzaldehyde, ethyl acetoacetate and urea<sup>a</sup>

No.	Catalyst	Catalyst (mol%)	Solvent	Yield of <b>2a</b> (%) <sup>b</sup>	TON <sup>c</sup>
1	None	_	CH <sub>3</sub> CN	00	_
2	$Cu(OTf)_2$	0.5	CH <sub>3</sub> CN	85	170
	$Cu(OTf)_2$	1	_	90	90
	$Cu(OTf)_2$	1	CH <sub>3</sub> CN	95, 90, 88, 85, 80 <sup>d</sup>	95, 90, 88, 85, 80
	$Cu(OTf)_2$	1	THF	62	62
	$Cu(OTf)_2$	1	EtOH	83	83
	$Cu(OTf)_2$	1	$H_2O$	05	05
	Cu(OTf) <sub>2</sub>	5	CH <sub>3</sub> CN	95	19
	Cu(OTf) <sub>2</sub>	10	CH <sub>3</sub> CN	94	9.4
3	CuCl	5	CH <sub>3</sub> CN	20	04
4	CuCN	5	CH <sub>3</sub> CN	30	06
5	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	5	CH <sub>3</sub> CN	05	01
6	CuSO <sub>4</sub> ·5H <sub>2</sub> O	5	CH <sub>3</sub> CN	00	00

<sup>a</sup> Reaction conditions:<sup>4</sup> benzaldehyde (2 mmol), urea (2 mmol), ethyl acetoacetate (2 mmol), 25°C.

<sup>b</sup> Isolated yield after recrystallization.

<sup>c</sup> TON=turn-over number (defined as: mmol of product/mmol of catalyst).

<sup>d</sup> Catalyst was reused at least five times.

conducted under 'solvent free' conditions. Among the copper salts screened,  $Cu(OTf)_2$  showed excellent activity in terms of yield in producing the required product.

In order to gauge the scope of these conditions, several aromatic and aliphatic aldehydes were examined under the optimized conditions using 1 mol% of Cu(OTf)<sub>2</sub>.

Table 2. Cu(OTf)<sub>2</sub>-catalyzed synthesis of 3,4-dihydropyrimidin-2(1H)-ones<sup>a</sup>



No.	R	Temp. (°C)	Time (h)	Product 2a-x		TON <sup>c</sup>
				Yield <sup>b</sup> (%)	Mp (°C)	
a	Ph	25	6	95	200–202	95
b	$2-Cl-C_6H_4$	50	9	70	216-218	70
c	$3-Cl-C_6H_4$	60	9	80	190-193	80
d	$4-Cl-C_6H_4$	50	4	85	212-213	85
e	$4-OMe-C_6H_4$	40	5	90	200-201	90
f	$2-OH-C_6H_4$	50	6	80	200-202	80
g	$4-OH-C_6H_4$	40	5	90	199-200	90
h	$3 - O_2 N - C_6 H_4$	60	9	75	226-225	75
i	$4-NO_2-C_6H_4$	50	6	80	207-209	80
j	$4-NC-C_6H_4$	70	12	60	219-222	60
k	$4 - Me_2 N - C_6 H_4$	60	9	65	230-232	65
1	3-OMe-4-OH-C <sub>6</sub> H <sub>3</sub>	50	6	85	204-205	85
m	3-OH-4-OMe-C <sub>6</sub> H <sub>3</sub>	50	6	85	185-187	85
n	$3,4-(OMe)_2-C_6H_3$	50	6	85	175-177	85
<b>0</b> <sup>5</sup>	$3,4,5-(OMe)_3-C_6H_2$	50	6	85	180-182	85
р	3,4-(O-CH <sub>2</sub> -O)-C <sub>6</sub> H <sub>3</sub>	50	6	85	188-189	85
$\mathbf{q}^5$	3-(Cyclopentyloxy)-4-OMe-C <sub>6</sub> H <sub>3</sub>	50	6	80	185-188	80
r	$2-OH-4-Cl-C_6H_3$	70	9	65	240-243	65
s	2-OH-4-Br-C <sub>6</sub> H <sub>3</sub>	70	9	80	195-196	80
t	$3-NO_2-4-Me-C_6H_3$	60	9	70	218-219	70
u	1-Naphthyl	50	6	85	246-248	85
v	2-Furyl	70	6	70	203-205	70
w	$c - C_6 H_{11}$	70	12	60	236-237	60
x	$n - C_9 H_{19}$	70	12	60	122–124	60

<sup>a</sup> Reaction conditions:<sup>4</sup> aldehyde (2 mmol), urea (2 mmol), ethyl acetoacetate (2 mmol), Cu(OTf)<sub>2</sub> (1 mol%), 25°C.

<sup>b</sup> Isolated yield after recrystallization.

<sup>c</sup> TON=turn over number (defined as: mmol of product/mmol of catalyst).



Scheme 2. Cu<sup>2+</sup>-activation in three-component coupling for Biginelli reaction.

The results are shown in Table 2. In all cases studied, the three-component reaction proceeded smoothly to give the corresponding 3,4-dihydropyrimidin-2(1H)ones in high yields. Most importantly, aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents including hydroxy groups reacted efficiently giving excellent yields. It was established that the mechanism of this reaction involves, at first, the formation of activated acylimine 3 so that addition of enolate 4 is facilitated to afford intermediate 5 which then undergoes facile condensation to give 3,4-dihydropyrimidin-2(1H)-ones 2 (Scheme 2) [the formation of 3 and 5 was confirmed in our studies by in situ <sup>1</sup>H and <sup>13</sup>C NMR experiments in  $CD_3OD$  at 25°C].

In conclusion, we describe a simple modification of the Biginelli 3,4-dihydropyrimidin-2(1*H*)-one synthesis using Cu(OTf)<sub>2</sub> as a reusable catalyst. Excellent yields, recycling of the catalyst with negligible loss of activity, and the application to a variety of substituted/function-alized aryl aldehydes are some of the salient features of this reaction. It is noteworthy that many 3,4-dihydropyrimidin-2(1*H*)-ones **2** and their derivatives are medicinally important as calcium channel blockers, antihypertensive agents,  $\alpha$ -1a-antagonists and anti-HIV agents.<sup>6</sup>

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- 4. General experimental procedure: A 25 ml RB flask was charged with aldehyde 1a-x (2 mmol), urea (0.120 g, 2 mmol), ethyl acetoacetate (0.260 g, 2 mmol), Cu(OTf)<sub>2</sub> ( 7 mg, 1 mol%) and acetonitrile (5 ml). The resulting reaction mixture was stirred at given temperature in (see Table 2). After the reaction was complete (monitored by TLC), the reaction mixture was cooled to room temperature and filtered through a sintered funnel. The crude product was further purified by recrystallization (EtOH or *i*PrOH) to afford pure 3,4-dihydropyrimidin-2(1*H*)-ones **2a**-x.
- 5. All the compounds listed in Table 2 were thoroughly characterized by <sup>1</sup>H NMR, FT-IR and MS spectroscopy. Spectral data for selected new compounds: 5-Ethoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (20): mp 180–182°C (recrystallized from EtOH); IR (THF) 3227, 3102, 2925, 2840, 1705, 1646, 1610, 1581, 1512 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, DMSO- $d_6$ ):  $\delta$  1.13 (t, J = 7.0 Hz, 3H), 2.25 (s, 3H), 3.72 (s, 9H), 4.02 (q, J=6.66 Hz, 2H), 5.13 (s, 1H), 6.53 (s, 2H), 7.75 (s, 1H), 9.23 (s, 1H); <sup>13</sup>C NMR (200 MHz, DMSO- $d_6$ ):  $\delta$  14.26, 17.87, 54.11, 56.09, 59.40, 60.17, 99.54, 104.03, 140.60, 148.54, 152.55, 152.99, 165.63; MS m/z (% rel. int.): 350 (M<sup>+</sup>, 68), 335 (9), 321 (50), 304 (23), 277 (41), 261 (22), 238 (69), 222 (22), 195 (100), 183 (72), 168(23), 155 (45), 137 (75), 125 (52), 110 (40), 77 (32), 66 (41). Anal. calcd for C17H22N2O6: C, 58.27; H, 6.32; N, 7.99. Found: C, 58.32; H, 6.22; N, 8.01%.

5-Ethoxycarbonyl-4-(3-cyclopentoxy-4-methoxyphenyl)-6methyl-3,4-dihydropyrimidin-2(1*H*)-one (**2q**): mp 185– 188°C (recrystallized from *i*PrOH); IR (THF) 3225, 3101, 2922, 2845, 1707, 1649, 1615, 1580, 1510 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  1.11 (t, *J*=8.0 Hz, 3H), 1.70 (m, 9H), 2.26 (s, 3H), 3.74 (s, 3H), 4.01 (q, *J*=7.33 Hz, 2H), 4.66 (broad, 1H), 5.08 (d, 1H), 6.70–6.90 (m, 3H), 7.68 (s, 1H), 9.16 (s, 1H); <sup>13</sup>C NMR (200 MHz, DMSO- $d_6$ ):  $\delta$  14.23, 17.83, 23.60, 3242, 53.59, 55.91, 59.37, 80.06, 99.98, 112.7, 113.88, 118.40, 137.51, 147.07, 148.06, 149.20, 152.55, 154.68, 165.63. Anal. calcd for C<sub>20</sub>H<sub>26</sub>N<sub>2</sub>O<sub>5</sub>: C, 64.15; H, 6.99; N, 7.48. Found: C, 64.21; H, 6.85; N, 7.51%.

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