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Highly Efficient Solvent-Free Synthesis of Dihydropyrimidinones Catalyzed by Zinc Oxide

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Abstract: A simple, efficient and practical procedure for the Biginelli reaction using zinc oxid (ZnO) as a novel and reusable catalyst is described under solvent-free conditions in high yields. The use of this agent is characterized by remarkable reactivity, moderate costs, low toxicity and simple work up procedures.

Keywords: Cyclocondensation, solvent-free, 1,2,3,4-tetrahydropyrimidine, zinc oxide

INTRODUCTION

The demand for structural diversification in compound libraries for screening in drug discovery is the driving force behind the development of new methodologies and structural motifs. The cyclocondensation of acetoacetic esters with aromatic aldehydes and (thio)urea, known as the Biginelli reaction, has attracted considerable attention in recent years. The resulting 1,2,3,4-tetrahydropyrimidine derivatives have been shown to possess a variety of interesting pharmacological properties.^[1] Consequently, synthesis of the heterocyclic nucleus contained in such compounds has gained importance. Many synthetic methods for the synthesis of this heterocyclic scaffold are now available.^[2–14] Some of them are really very fascinating from a synthetic chemist's point. Despite

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Scheme 1. ZnO-catalyzed Biginelli reaction.

their tremendous success, however, some drawbacks still remain. For example, some of the catalysts are expensive, complex, or unavailable, and organic solvents are always used.

With the increase of environmental consciousness in chemical research and industry, the solvent-free Biginelli reaction has attracted much attention and received good results recently.^[8,15,16] Herein we report a general and practical route for the preparation of 3,4-dihydropyrimidin-2-(1H)-ones using zinc oxide as a mild and reusable catalyst (Scheme 1).

Zinc oxide (ZnO), a very inexpensive and easily available Lewis acid catalyst, has been widely used in organic reactions, but it has not been carefully studied as a catalyst in the Biginelli condensation until now, except for a few mentions in the literature.^[17]

To be able to carry out such a Biginelli condensation in a more efficient way, minimizing the time, temperature, and amount of catalyst, we performed a set of preliminary experiments on benzaldehyde as model substrate, ethyl acetoacetate, and urea in the presence of different amounts of zinc oxide under solvent-free conditions at 80°C.

Entry	ZnO (mmol)	Yield (%) ^b	
1	0.05	43	
2	0.1	75	
3 ^{<i>c</i>}	0.125	97, 95, 92	
4	0.25	98	

Table 1. Effect of increasing amount of ZnO on the preparation of 3,4-dihydropyrimidin-2-(1*H*)-ones^{*a*}

^{*a*}Reaction conditions: The reactions were performed with benzaldehyde (1 mmol), ethyl acetoacetate (1.3 mmol), and urea (1.5 mmol) for 19 min at 80° C under solvent-free conditions.

^bIsolated yield.

^cCatalyst was recycled three times.

Solvent-Free Synthesis of Dihydropyrimidinones

The results are depicted in Table 1. As shown, a ratio of 1:1.3: 1.5:0.125 benzaldehye/1,3-dicarbonyl/urea/ZnO was found to be optimal for the preparation of 3,4-dihydropyrimidin-2-(1*H*)-ones. The best conversion was obtained when the reaction was run at 80°C. An increase in the reaction temperature and time did not improve the yields significantly.

Although acetonitrile and ethanol were found to be effective, considering stringent environmental regulations, solvent-free reactions are desired. Therefore, we intended the Biginelli reaction to be under solventfree conditions. The activity of the recycled catalyst was also examined under the optimized conditions, and the desired product was obtained in 97, 95, and 92% yields after one to three runs, respectively (Table 1, entry 3).

Table	2. Zinc	oxide-catalyzed	synthesis	of	dihydropyrimidinones	under
solvent	t-free con	ditions				

Entry	R	R′	Х	Time (min)	Yield (%) ^{<i>a,b</i>}
1	C_6H_5	OEt	0	19	97
2	4-MeC ₆ H ₄	OEt	Ο	15	96
3	$4-OHC_6H_4$	OEt	Ο	12	94
4	$4-NO_2C_6H_4$	OEt	Ο	11	95
5	$4-NMe_2C_6H_4$	OEt	Ο	20	95
6	4-MeOC ₆ H ₄	OEt	Ο	15	98
7	$4-ClC_6H_4$	OEt	Ο	12	95
8	CH_3	OEt	Ο	17	75
9	CH ₃ CH ₂ CH ₂	OEt	Ο	18	60
10	$4 - MeC_6H_4$	OEt	S	24	96
11	$4 - NO_2C_6H_4$	OEt	S	16	96
12	4-MeOC ₆ H ₄	OEt	S	20	95
13	$4-ClC_6H_4$	OEt	S	14	95
14	C_6H_5	OEt	S	35	98
15	$4-FC_6H_4$	OMe	0	8	97
16	$4-ClC_6H_4$	OMe	S	10	97
17	4-MeOC ₅ H ₄	Me	Ο	10	95
18	$4 - NO_2C_6H_4$	Me	Ο	6	96
19	$4 - FC_6H_4$	Me	Ο	8	94
20	C_6H_5	Me	S	8	96
21	$2-ClC_6H_4$	Me	S	11	96
22	$4-\text{MeOC}_6\text{H}_4$	Me	S	18	95

^{*a*}The products were characterized by comparison of their spectroscopic and physical data with authentic samples synthesized by reported procedures.

^bYields refer to pure isolated products.

To extend the scope of the reaction and to generalize the procedure, we investigated the reactions of a series of aromatic aldehydes with (thio)urea and 3-oxo esters or acetylacetone under the optimized reaction conditions. In all cases studied, the three-component reaction proceeded smoothly to give the corresponding 3,4-dihydropyrimidin-2(1H)-ones in satisfactory yields. Aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents reacted efficiently and gave excellent yields. Even for aliphatic aldehydes, which usually show extremely poor yields in the Biginelli reaction, 75% and 60% yields of the corresponding dihydropyrimidin-2(1H)-ones **8** and **9** could be obtained. In addition, thiourea were also used with similar success to provide the corresponding 3,4-dihydropyrimidin-2(1H)-thiones (Table 2).

A comparison of the catalytic efficiency of ZnO with selected previously known catalysts is shown in Table 3 to demonstrate that the present protocol is indeed superior to several of the other protocols.

In conclusion, we have described a new and simple modification of the Biginelli reaction using inexpensive ZnO as a catalyst in solventfree conditions. The method offers several advantages including catalyst recyclability, excellent yields, environmentally friendly procedure, short reaction times, simple work up procedure, and easy isolation, which make it a useful process for the synthesis of dihydropyrimidiones as well as the thio-derivatives. Hence, it is a useful addition to the existing methods.

Entry	Reagent/catalyst	Time	Yield (%)
1	ZnO	19 min	97
	$H_{3}PMo_{12}O_{40}/CH_{3}CN/80^{\circ}C^{[18]}$	1 h	93
	ClCH ₂ COOH/solvent-free/90°C ^[19]	3 h	92
	$Cu(BF_4)_2 \cdot xH_2O/solvent-free/rt^{[20]}$	30 min	90
2	ZnO	15 min	96
	ClCH ₂ COOH/solvent-free/90°C ^[19]	3 h	86
	$H_{3}PW_{12}O_{40}/SiO_{2}/CH_{3}CN/80^{\circ}C^{[21]}$	50 min	97
6	ZnO	15 min	98
	CH ₃ COOH/MW ^[22]	7 min	84
	HBF_4 /solvent-free/45°C ^[23]	45 min	92
7	ZnO	12 min	95
	TCCA ^a /Ethnol/reflux ^[24]	8 h	95
	HPVMo ₁₁ /EtOH/80°C ^[25]	6 h	95

Table 3. Comparison of protocols for the synthesis of dihydropyrimidin-2-(1H) ones

^aTrichloroisocyanuric acid.

EXPERIMENTAL

Zinc oxide as well as urea, thiourea, β -dicarbonyls, and all the aldehydes employed and substrates are commercial products (Merck) and were used without further purification. Melting points were determined in a capillary tube and are not corrected. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker-200 NMR spectrometer using tetramethylsilane (TMS) as internal standard.

General Procedures for One-Pot Preparation of 3,4-Dihydropyrimidiones or Its Derivatives Using ZnO as a Catalyst

A mixture of aldehyde (1 mmol), β -dicarbonyl (1.3 mmol), urea or thiourea (1.5 mmol), and ZnO (0.125 mmol, 0.01 g) was heated at 80°C under stirring for the time indicated in Table 2. Then, ethanol (15 mL) was added to the reaction mixture, and it was stirred for 5 min at 80°C. The reaction mixture was filtered to remove the catalyst, and the filtrate was poured into cold water. The solid was suction filtered, washed with cold water (20 mL × 2), filtered, and recrystallized from ethyl acetate/*n*-hexane to afford pure product.

All products are known compounds and characterized easily by comparison with authentic samples, except compounds **19**, **21**, and **22** (Table 2), whose spectral and analytical data are furnished.

Compound 19

Solid, mp 220°C; ¹H NMR (200 MHz, DMSO-d₆): δ = 9.23 (br, 1H), 7.86 (br, 1H), 7.11–7.31 (m, 5H), 5.26 (d, *J* = 3.48 Hz, 1H), 2.29 (s, COCH₃) 2.12 (s, CH₃); ¹³C NMR (50 MHz, DMSO-d₆): δ = 195, 152.48, 148.73, 128.92, 128.76, 115.86, 115.44, 110.08, 53.48, 30.80, 19.37. Anal. calcd. for C₁₃H₁₃N₂O₂F: C, 62.9; H, 5.3; N, 11.3. Found: C, 62.8; H, 5.4; N, 11.5.

Compound 21

Solid, mp 118°C; ¹H NMR (200 MHz, DMSO-d₆): δ = 10.31 (br, 1H), 9.60 (br, 1H), 7.18–7.34 (m, 3H), 7.39–7.44 (m, 1H), 5.65 (d, *J* = 3.72 Hz, 1H), 2.32 (s, COCH₃), 2.07 (s, CH₃); ¹³C NMR (50 MHz, DMSO-d₆): δ = 195, 174.34, 145.33, 140.16, 132.29, 130.16, 129.52, 128.36, 110.15, 52, 30.72, 18.60. Anal. calcd. for C₁₃H₁₃N₂SOCI: C, 55.6; H, 4.7; N, 10.0; S, 11.42. Found: C, 55.4; H, 4.8; N, 9.8; S, 11.5.

Compound 22

Solid, mp 173°C; ¹H NMR (200 MHz, DMSO-d₆): $\delta = 10.30$ (br, 1H), 9.75 (br, 1H), 7.20 (d, J = 8.41 Hz, 2H), 6.95 (d, J = 8.41 Hz, 2H), 5.27 (d, J = 3.72 Hz, 1H), 3.86 (s, OCH₃), 2.40 (s, COCH₃) 2.17 (s, CH₃); ¹³C NMR (50 MHz, DMSO-d₆): $\delta = 195.25$, 174.15, 159.12, 144.63, 135.42, 128.21, 114.34, 110.79, 55.46, 53.67, 30.63, 18.55. Anal. calcd. for C₁₄H₁₆N₂SO: C, 60.8; H, 5.8; N, 10.1; S, 11.6. Found: C, 60.6; H, 6.0; N, 10.3; S, 11.5.

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