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Efficient Biginelli Reaction Catalyzed by Sulfamic Acid or Silica Sulfuric Acid under Solvent-Free Conditions

Wei-Yi Chen [a] , Su-Dong Qin [b] & Jian-Rong Jin [a]

[a] College of Chemistry and Chemical Engineering of Suzhou University, Suzhou, China

[b] Technical Department of JiangShan Pharmaceutical Corporation, JingJiang, China

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Efficient Biginelli Reaction Catalyzed by Sulfamic Acid or Silica Sulfuric Acid under Solvent-Free Conditions

Wei-Yi Chen
College of Chemistry and Chemical Engineering of Suzhou University, Suzhou, China

Su-Dong Qin
Technical Department of JiangShan Pharmaceutical Corporation, JingJiang, China

Jian-Rong Jin
College of Chemistry and Chemical Engineering of Suzhou University, Suzhou, China

Abstract: Sulfamic acid efficiently catalyzes the three-component condensation reaction of aldehydes, 1,3-dicarbonyl compounds, and urea/thiourea under solvent-free conditions to afford the corresponding dihydropyrimidinones and thio-derivatives in high yields. Silica sulfuric acid is also found to be an efficient catalyst for the Biginelli reaction under solvent-free conditions. Compared to the classical Biginelli reaction conditions, this new method consistently has the advantage of giving good yields and requiring short reaction times.

Keywords: aldehyde, Biginelli reaction, silica sulfuric acid, solvent-free, sulfamic acid

3,4-Dihydropyrimidin-2(1H)-ones and related compounds have been found to exhibit a wide spectrum of biological effects,[1,2] including antiviral,

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Address correspondence to Wei-Yi Chen, College of Chemistry and Chemical Engineering of Suzhou University, Suzhou, China. E-mail: suzhoucwy@163.com

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antitumor, antibacterial, and anti-inflammatory activities. In addition, the dihydropyrimidine-5-carboxylate core unit is found in many marine natural products including batzelladine alkaloids, which are found to be potent HIVgp-120-CD4 inbibitors.[3] So, the synthesis of this heterocyclic nucleus is of importance.

The simple and direct method originally reported by Biginelli[4] for the synthesis of dihydropyrimidinones involves three-component condensation reactions (i.e., aldehydes, β-ketoester, and urea) under strong acidic conditions with low yields (20–50%), and so it needs improving into an efficient procedure. In recent years, interest in this reaction has increased rapidly, and many synthetic methods for preparing these compounds have been reported. For example, modifications and improvements using Lewis acids as well as protic acid promoters such as $Cu(OTf)_2$,[5] $BF_3 \cdot OEt_2$,[6] InX_3 ($X = Cl$, Br),[7] montmorillonite (KSF),[8] $FeCl_3 \cdot 6H_2O$,[9] $Mn(OAc)_3 \cdot 2H_2O$,[10] $LiClO_4$,[11] H_2SO_4,[12] $Zn(NH_2SO_3)_2$,[13] and ionic liquid[14] have been reported. In addition, microwave irradiation is also found to accelerate the reaction.[15] However, some of these one-pot procedures generally require strong protic or Lewis acids, prolonged reaction time, high temperature, stoichiometric amounts of catalysts, and the use of toxic and inflammable solvents, and give unsatisfactory yields. Therefore, the discovery of a milder and more efficient procedure for the synthesis of dihydropyrimidinone is of prime importance. There is a need to develop new methods using less hazardous solvents or, even better, those that do not need solvents at all. More recently, some catalysts have been used for this transformation under solvent-free conditions.[16] This prompted us to seek an alternative and solvent-free method of synthesis of these biologically significant compounds.

Recently, it was shown that sulfamic acid (SA) and silica sulfuric acid (SSA) have potential to be used as substitutes for conventional acidic catalytic materials. Sulfamic acid and silica sulfuric acid have been extensively used as catalysts for many organic reactions by now,[17] and they also have been used in the synthesis of 3,4-dihydropyrimidin-2(1H)-ones. In this article, we describe an efficient and mild Biginelli reaction catalyzed by sulfamic acid or silica sulfuric acid under solvent-free conditions in a short time.

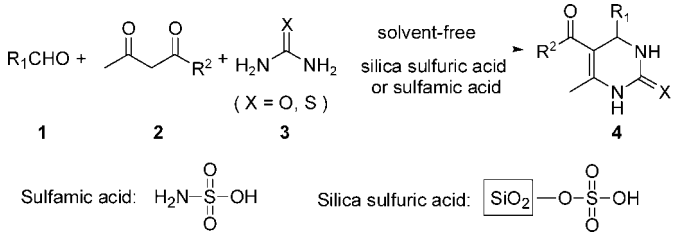
To study the generality of this process, several examples were studied (Table 1). The results showed that the efficiency and the yield of the reaction in solution were less than those obtained under solvent-free conditions. The use of 30 mol% of the catalyst was sufficient to promote the reaction. Higher amounts of the catalyst did not improve the yields. When the reaction was investigated at 120°C, the reaction was completed with higher yield and in shorter reaction time (Table 1, entries 7, 10). Obviously, the temperature and the catalyst have important effects on the reaction. The best result was obtained when the reaction was carried out in the presence of a catalytic amount of sulfamic acid or silica sulfuric acid at 120°C under solvent-free conditions (Scheme 1).

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

Entry	Catalyst	Amount of catalyst (mol%)	Solvent	Temp. (°C)	Time	Yield of **4a** (%)
1	**SA**	20	EtOH	Reflux	8 h	80
2	—	—	—	100	20 min	70
3	**SA**	10	—	100	20 min	86
4	**SA**	20	—	100	15 min	88
5	**SA**	30	—	100	15 min	89
6	**SA**	40	—	100	10 min	92
7	**SA**	30	—	120	8 min	94
8	**SSA**	30	EtOH	Reflux	6 h	90
9	**SSA**	30	—	100	15 min	92
10	**SSA**	30	—	120	10 min	95

Having optimized the reaction conditions, we extended the three-component condensation reaction to a wide variety of aldehydes. The results obtained are shown in Table 2.

As can be seen from Table 2, aldehydes, 1,3-dicarbonyl compounds, and urea or thiourea in the presence of a catalytic amount of sulfamic acid or silica sulfuric acid gave the corresponding dihydropyrimidinones and thio-derivatives in good yields under solvent-free conditions. In most cases, the products were extracted from the reaction mixture with ethyl acetate. The crude products were purified by recrystallization from ethanol. Meanwhile the catalyst can be recovered by simple filtration and can be recycled in subsequent reactions with comparable activity. An important feature of this method is that aromatic aldehydes carrying either electron-donating or electron-withdrawing groups afforded high yields of products in high purity. In addition, cyclohexanecarboxaldehyde, which replaced the aromatic aldehyde as one of the substrates, was tested, and the corresponding products were produced in good yields under the same reaction conditions



Scheme 1.

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Table 2. SA/SSA-catalyzed Biginelli reaction under solvent-free conditions[a]

Product 4	R_1	R_2	X	Catalyst	Time (min)	Yield (%)[b]	Ref.
4a	C_6H_5	OC_2H_5	O	**SA**	8	94	[11]
4b	4-$CH_3OC_6H_4$	OC_2H_5	O	**SA**	10	86	[9]
4c	4-ClC_6H_4	OC_2H_5	O	**SA**	10	91	[9]
4d	4-$(CH_3)_2NC_6H_4$	OC_2H_5	O	**SA**	10	84	[9]
4e	4-$O_2NC_6H_4$	OC_2H_5	O	**SA**	8	92	[11]
4f	*c*-C_6H_{11}	OC_2H_5	O	**SA**	12	80	[11]
4g	C_6H_5	OC_2H_5	S	**SA**	8	91	[15]
4h	4-$CH_3OC_6H_4$	OC_2H_5	S	**SA**	8	93	[15]
4i	4-$O_2NC_6H_4$	OC_2H_5	S	**SA**	8	95	[15]
4j	4-ClC_6H_4	OC_2H_5	S	**SA**	8	96	[15]
4k	*c*-C_6H_{11}	OC_2H_5	S	**SA**	10	81	[20]
4l	C_6H_5	CH_3	O	**SA**	8	91	[18]
4m	3-$O_2NC_6H_4$	CH_3	O	**SA**	8	92	[18]
4n	*c*-C_6H_{11}	CH_3	O	**SA**	10	80	[20]
4o	C_6H_5	CH_3	S	**SA**	8	95	[19]
4p	4-$CH_3OC_6H_4$	CH_3	S	**SA**	8	94	[19]
4q	4-ClC_6H_4	CH_3	S	**SA**	8	94	[19]
4r	4-$O_2NC_6H_4$	CH_3	S	**SA**	8	93	[20]
4a	C_6H_5	OC_2H_5	O	**SSA**	10	95	[11]
4b	4-$CH_3OC_6H_4$	OC_2H_5	O	**SSA**	10	91	[9]
4e	4-$O_2NC_6H_4$	OC_2H_5	O	**SSA**	10	92	[11]
4g	C_6H_5	OC_2H_5	S	**SSA**	10	89	[15]
4h	4-$CH_3OC_6H_4$	OC_2H_5	S	**SSA**	10	94	[15]
4i	4-$O_2NC_6H_4$	OC_2H_5	S	**SSA**	10	88	[15]
4k	*c*-C_6H_{11}	OC_2H_5	S	**SSA**	12	81	[20]

[a]All products were characterized by ^{1}H NMR, IR, and mass spectroscopy.
[b]Isolated yields.

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(**4f**, **4k**, **4n**). The structure of **4k** was further confirmed by single-crystal X-ray crystallography (Fig. 1). (Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 219835 for compounds **4k**. Copies of this information may be obtained free of charge from the director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [E-mail: linstead@ccdc.cam.ac.uk or deposit@ccdc.cam.ac.uk; Fax: +44 (1223)336033]. Structural parameters for **4k**: data collection: Rigaku Mercury CCD area detector; radiation: MoK. Wavelength = 0.71070 Å; crystal size: $0.4 \times 0.3 \times 0.12\ mm^3$; crystal system: triclinic; space group: P-1 (#2); unit cell: a = 8.5643(2) Å, b = 13.7994(2) Å, c = 14.4627 Å, $\alpha = 98.74(2)^\circ$.)

In conclusion, we have demonstrated a very simple, efficient, and practical method for the synthesis of dihydropyrimidinones and thio-derivatives through a one-pot, three-component condensation of aldehydes,

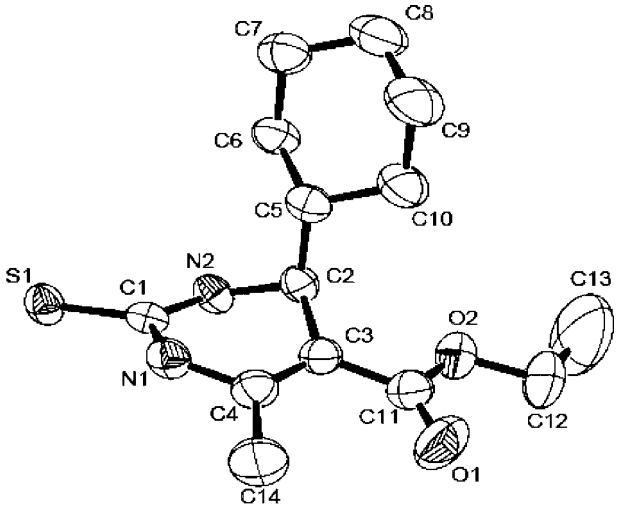

Figure 1. X-ray structure of the title compound **4k**.

1,3-dicarbonyl compounds, and urea or thiourea catalyzed by sulfamic acid or silica sulfuric acid under solvent-free conditions. The main features of our new reaction are as follows: (1) the procedure is operationally simple and can furnish a wide variety of dihydropyrimidinones and thio-derivatives in good yields; (2) the condensation reaction could be performed exclusively using cheap, commercially available chemicals; (3) the catalyst could be recycled with comparable activity; and (4) the method is cost-effective and environmentally benign.

EXPERIMENTAL

Apparatus and Analysis

Melting points were recorded in open capillaries and are uncorrected. ^{1}H NMR (400 MHz) spectra were obtained for solution in DMSO-d_6 with Me4Si as internal standard on a Varian-Inova-400 spectrometer. IR spectra were obtained on a Nicolet FT-IR500 spectrophotometer using KBr pellets. High-resolution mass spectra were obtained using GCT-TOF instrument. The X-ray diffraction was performed on a Rigaku Mercury CCD X-ray diffractometer. Ethyl acetoacetate was purified by distillation prior to use.

General Procedure

A mixture of benzaldehyde (2 mmol), ethyl acetoacetate (2 mmol), urea (3 mmol), and silica sulfuric acid (0.6 mmol) was stirred at 120°C under

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solvent-free conditions for 10 min. After completion of the reaction, the mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo, and the solid product **4a** was recrystallized from hot ethanol. Mp 204–205°C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.08 (t, $J = 6.4$ Hz, 3H, CH_3), 2.31 (s, 3H, CH_3), 4.02 (q, $J = 6.4$ Hz, 2H, CH_2), 5.10 (s, 1H, CH), 7.11–7.35 (m, 5H, ArH), 9.63 (s, 1H, NH), 10.38 (s, 1H, NH); IR (KBr) ν: 3242, 3122, 2956, 1724, 1703, 1645 cm^{-1}; HRMS calcd. for $C_{14}H_{16}N_2O_3$: 260.1161, found: 260.1158.

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