

Short communication

One-pot synthesis of 3,4-dihydropyrimidin-2(1H)-(thio)ones using strontium(II) nitrate as a catalyst

Chenjiang Liu, Jide Wang*, Yanping Li

Key Laboratory of Petroleum and Gas Fine Chemicals, Educational Ministry of China, College of Chemistry and Chemical Engineering, Xinjiang University, Urumqi 830046, PR China

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Abstract

A simple, efficient method for the one-pot Biginelli condensation reaction of aldehydes, ethyl acetoacetate and urea or thiourea employing strontium(II) nitrate as a novel catalyst is described in good yields. The catalyst exhibited remarkable reactivity.

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1. Introduction

The Biginelli reaction was first reported by the Italian chemist Biginelli in 1893 [1], and involves the synthesis of 3,4-dihydropyrimidin-2(1H)-ones by a very simple one-pot condensation reaction of an aldehyde, β -ketoester and urea in ethanol. Dihydropyrimidinones have attracted increasing interest due to their significant pharmaceutical and therapeutic properties [2], such as antiviral, antitumor, antibacterial and antiinflammatory activities. Appropriately functionalized dihydropyrimidinones have been successfully used as the integral backbones of several calcium channel blockers [3], adrenergic [4], neuropeptide Y (NPY) antagonists [5] and antihypertensive agents [6]. Moreover, some marine natural products containing the dihydropyrimidinone-5-carboxylate unit such as the alkaloid Batzelladine B have been found to be potent HIV gp-120-CD4 inhibitors [7]. Therefore, synthesis of dihydropyrimidinones and their derivatives is drawing more and more attention from organic and medicinal chemists.

However, the original one-pot, one-step condensation protocol often suffers from the drawbacks including longer reaction times, harsh conditions and lower yields, particularly when substituted aromatic and aliphatic aldehydes are employed. The development of efficient and environmentally acceptable syn-

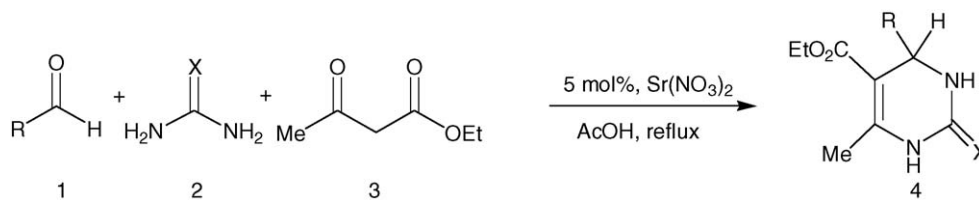
thetic methods is an important task of modern chemistry. In the recently, several improved procedures for the synthesis of dihydropyrimidinones have been reported, either by the development of novel, but more complex, multi-step strategies [8], or by modification of the classical one-pot condensation approach itself, including the use of different kinds of Lewis acid catalysts as well as protic acids, such as FeCl_3 [9], ZnCl_2 , CuCl_2 and NiCl_2 [10], ZnI_2 [11], VCl_3 [12], indium(III) halides [13], NH_4Cl [14], ZrCl_4 [15], H_3BO_3 [16], $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ [17], silica sulfuric acid [18], LiClO_4 [19], $\text{Sr}(\text{OTf})_2$ [20], $\text{In}(\text{OTf})_3$ [21], $\text{SiO}_2\text{-NaHSO}_4$ [22], $\text{NH}_2\text{SO}_3\text{H}$ [23].

In addition, the ionic liquids [24], polymer-supported reagents [25] were also utilized as the catalytic condition. Due to the importance of Biginelli reaction products, the discovery and introduction of milder, faster conditions using new catalysts has been under attention. In this paper, we wish to describe a procedure for the synthesis of 3,4-dihydropyrimidin-2(1H)-(thio)ones via condensation of aldehyde, ethyl acetoacetate and urea or thiourea catalyzed by strontium(II) nitrate (Scheme 1).

2. Experiments

All compounds were characterized by IR, ^1H NMR spectra and elemental analysis. The IR spectra were obtained as potassium bromide pellets with a FTS-40 spectrometer (BIO-RAD, U.S.A.). The ^1H NMR spectra were obtained on a Varian Inova-400 spectrometer using CDCl_3 or $\text{DMSO-}d_6$ as solvent (shown

* Corresponding author. Tel.: +86 991 8582807; fax: +86 991 8582807.
E-mail address: cjliuxj@126.com (J. Wang).



Scheme 1.

in details in data part) and TMS as an internal standard, chemical shifts are given in ppm. Elemental analysis (C, H, N) was performed on a Perkin-Elmer Analyzer 2400. Melting points were determined using a Büchi B-540 instrument. All melting points are uncorrected.

2.1. General procedure for the synthesis of 3,4-dihydropyrimidin-2(1H)-(thio)ones

General procedure for one-pot preparation of 3,4-dihydropyrimidin-2(1H)-(thio)ones **4** using $\text{Sr}(\text{NO}_3)_2$ as a catalyst is that a mixture of aldehyde (2 mmol), ethyl acetoacetate (2 mmol), urea or thiourea (3 mmol) and $\text{Sr}(\text{NO}_3)_2$ (0.1 mmol) was refluxing at 100°C in glacial acetic acid (15 mL) for 6 h without stirring. The completion of the reaction was monitored by TLC. After cooling, the reaction mixture was poured onto crushed ice (50 g) and stirred for 5 min. The separated solid was filtered under suction, washed with cold water (50 mL) and then recrystallized from ethanol to afford the pure product.

All products (except **4l**) are known compounds, characterized by mp, IR, ^1H NMR spectra and elemental analysis. Data for **4l**: mp $218\text{--}220^\circ\text{C}$. ^1H NMR (DMSO- d_6 , 400 MHz): δ 1.12 (t, $J=7.2$ Hz, 3H, $\text{CH}_3\text{-CH}_2\text{O}$), 2.28 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 4.02 (q, $J=7.2$ Hz, 2H, $\text{CH}_3\text{CH}_2\text{-O}$), 5.09 (s, 1H, CH), 6.58–6.79 (m, 3H, arom CH), 9.06 (s, 1H, NH), 9.58 (bs, 1H, OH), 10.28 (bs, 1H, NH). ^{13}C NMR (DMSO- d_6 , 400 MHz): δ 13.91, 16.96, 53.21, 54.98, 59.51, 100.85, 113.77,

Table 2
 $\text{Sr}(\text{NO}_3)_2$ -catalyzed one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-(thio)ones^a

Entry	R	X	Yields ^b (%)	Time (h)	mp ($^\circ\text{C}$) ^c	
					Found	Reported (Ref.)
4a	C_6H_5	O	77.8	6	202–203	204 [21]
4b	4-HO- C_6H_4	O	69.5	6	231–233	226–228 [23]
4c	3- NO_2 - C_6H_4	O	83.3	6	226–228	230–232 [21]
4d	4-MeO- C_6H_4	O	69.7	6	203–204	202–204 [21]
4e	3-MeO-4-HO- C_6H_3	O	63.4	6	233–235	230–232 [21]
4f	$\text{C}_6\text{H}_5\text{CH}=\text{CH}$	O	87.5	6	234–236	237–239 [23]
4g	2-Furyl	O	53.0	6	205–207	208–209 [21]
4h	C_6H_5	S	54.8	6	206–208	208–209 [21]
4i	4-HO- C_6H_4	S	51.2	6	202–203	198–200 [15]
4j	3- NO_2 - C_6H_4	S	53.4	6	203–205	206–207 [20]
4k	4-MeO- C_6H_4	S	52.7	6	149–151	152–154 [21]
4l	3-MeO-4-HO- C_6H_3	S	52.1	6	147–149	
4m	$\text{C}_6\text{H}_5\text{CH}=\text{CH}$	S	58.6	6	243–245	244–246 [26]
4n	2-Furyl	S	50.1	6	183 (dec.)	185 (dec.) [26]

^a Reaction conditions: aldehyde (2 mmol), ethyl acetoacetate (2 mmol), urea or thiourea (3 mmol), $\text{Sr}(\text{NO}_3)_2$ (0.1 mmol), 100°C .

^b Isolated yield.

^c Melting points were uncorrected.

Table 1
Sr-catalyzed condensation of benzaldehyde, ethyl acetoacetate and urea^a

No.	Catalyst	Catalyst (mol%)	Time (h)	Yield of 4a ^b (%)
1	$\text{Sr}(\text{NO}_3)_2$	5	6	77.8
2	$\text{Sr}(\text{SO}_4)_2$	5	6	50.5
3	SrCl_2	5	6	51.6

^a Reaction conditions: benzaldehyde (2 mmol), ethyl acetoacetate (2 mmol), urea (3 mmol), HAc (15 mL), 100°C .

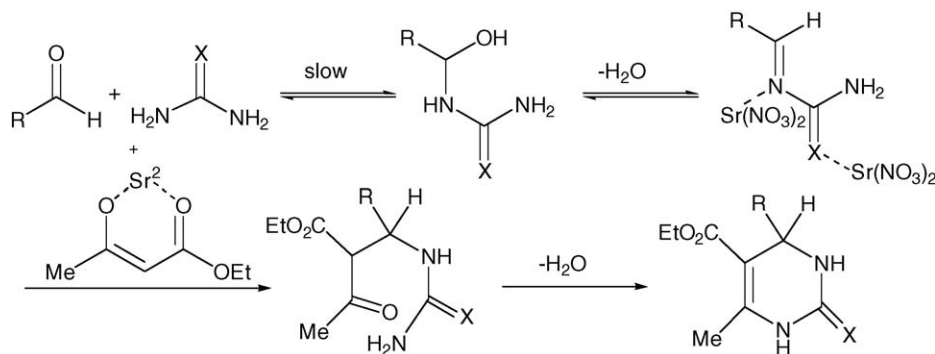
^b Isolated yield.

114.42, 127.54, 131.76, 135.52, 144.52, 158.64, 165.08, 173.66. IR (KBr): 3376, 3237, 3121, 2975, 1677, 1623, 1581, 1231, 1202 cm^{-1} . Anal. calcd. for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_4\text{S}$: C, 55.88; H, 5.63; N, 8.69. Found: C, 55.76; H, 5.56; N, 8.80.

3. Results and discussion

Results on the Biginelli reaction over different inorganic strontium(II) compounds of nitrate, chloride and sulfate catalysts are presented in Table 1. The results show that the catalytic activity of strontium(II) nitrate was better than those of the other two strontium(II) salt. It maybe the strong electron-withdrawing ability of nitrate ion, which reduced the density of the electron cloud round strontium(II) ion. So strontium(II) ion could accept electron easily, then made the reaction proceed smoothly.

In order to study the generality of this procedure, a series of Biginelli compounds were synthesized with similar opera-



Scheme 2.

tions. A summary of the results obtained is provided in Table 2. Under this novel conditions, the reaction time was significantly shortened from 18 h of the classical Biginelli method to 6 h, and the yields increased from 20–50% to 50–87%. Most importantly, aromatic aldehydes carrying either electron donating or withdrawing substituents afforded good yields of products. Acid sensitive aldehydes such as furfural is also worked well without the formation of any side products. Furthermore, thiourea has been used with similar success to provide the corresponding 3,4-dihydropyrimidin-2(1H)-thiones which are possessing good biological activities.

In order to get the best molar ratio of reaction materials, we also did the experiment with different ratios of aldehyde, ethyl acetoacetate, urea or thiourea and strontium(II) nitrate. We found that the reaction gave the best results when the molar ratio of reactants was 1:1:1.5:0.05, respectively.

A proposed reaction mechanism of Biginelli condensation via acyl imine intermediate is presented in Scheme 2, this intermediate is formed by the reaction of the aldehyde and urea or thiourea and then stabilized by $\text{Sr}(\text{NO}_3)_2$. Subsequent addition of ethyl acetoacetate enolate to the acylimine, followed by cyclization and dehydration, afforded the corresponding 3,4-dihydropyrimidin-2(1H)-(thio)ones.

4. Conclusion

In conclusion, we have shown that strontium(II) nitrate works as an excellent catalyst for the one-pot three-component synthesis of dihydropyrimidinones as well as the thio-derivatives. The method offers several advantages including good yields, short reaction times, simple work up procedure and easy isolation. Hence, it is an important addition to the other existing methods.

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