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Research Article

$Al(NO_3)_3 \cdot 9H_2O$: An Efficient Catalyst for the One-Pot Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones Both under Reflux or Solvent-Free Conditions

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$Al(NO_3)_3 \cdot 9H_2O$ efficiently catalyzes the three-component Biginelli reaction between an aldehyde, a β-dicarbonyl compound, and urea or thiourea in refluxing ethanol and solvent-free (SF) conditions to afford the corresponding dihydropyrimidinones in high yields. The advantages of this method involve the easy procedure, the environmentally friendly process, and the low cost of the Lewis acid catalyst.

1. Introduction

In 1893, the Italian chemist Pietro Biginelli reported a cyclocondensation reaction between ethylacetoacetate, benzaldehyde, and urea to obtain a heterocyclic system of 3,4-dihydropyrimidinones (DHPMs), which is known as Biginelli reaction [1]. Dihydropyrimidinones are known to exhibit a wide range of biological activities such as antiviral, antitumor, and antibacterial andante-inflammatory activities [2]. In addition, these compounds have emerged as potential calcium channel blockers, antihypertensive [3]. Furthermore, pyrimidin unit is found in many marine natural products including batzelladine alkaloids, which have been found to be HIVgp-120-CD_4 inhibitors [4]. Hence, the Biginelli reaction continues to attract the attention of organic chemists interested in finding milder and more efficient procedures for the synthesis of dihydropyrimidinones [5–7]. Synthetic strategies for the dihydropyrimidinone nucleus involve both one-pot and multistep approaches [8, 9]. At present, several general methods are known for the preparation of dihydropyrimidinones, using various Lewis and protic acids such as $BF_3{\cdot}OEt_2$ [10], $ZrCl_4$ [11, 12], $Sc(OTf)_3$ [13], zeolites [14–16], $SbCl_3$ [17], $CuCl_2{\cdot}2H_2O$ [18] trichloroisocyanuric acid (TCCA) [19], $RuCl_3$ [20], silica sulfuric acid (SSA) [21], and 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) [22]. However, some of these procedures suffer from disadvantages such as unsatisfactory yields, cumbersome product isolation procedures, and environmental pollution.

Therefore, there still exists a need for versatile, simple, and environmentally friendly processes whereby DHPMs may be formed under milder and practical conditions.

2. Experimental

2.1. General. Chemicals were purchased from Merck, Aldrich, and Acros companies and were used without further purification. All yields refer to isolated products. The purity determination of the substrates and reaction monitoring were accompanied by thin-layer chromatography (TLC) and visualized under ultraviolet (UV) light. Melting points were determined using Electrothermal 9100 instrument in open capillaries and are uncorrected. All compounds are well known and were identified by comparison of the spectroscopic data with those of the authentic samples.

2.2. Typical Reaction for the Synthesis of Biginelli Compounds in Refluxing Ethanol. A solution of ethyl acetoacetate

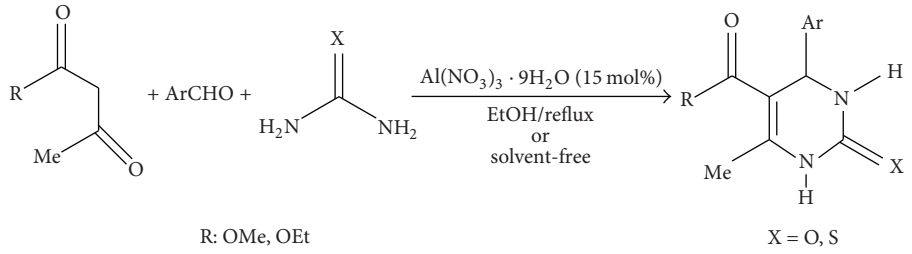

Figure 1: Aluminum nitrate-catalyzed synthesis of 3,4-dihydropyrimidin-2-ones/thiones.

Table 1: Influence amount of aluminum nitrate on the yield of ethyl-6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate in refluxing ethanol[a].

Entry	Catalyst amount (mol%)	Yield (%)
1	0	Negligible
2	5	70
3	10	85
4	15	92

[a]All reactions were carried out with 2 mmol of benzaldehyde, 2 mmol ethyl acetoacetate, and 3 mmol urea in 5 mL of ethanol in the presence of different amount of aluminum nitrate in ethanol under reflux condition for 7 h.

Table 2: Synthesis of ethyl-6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrim-idine-5-carboxylate in the presence of $Al(NO_3)_3{\cdot}9H_2O$ in various solvents under reflux and solvent-free conditions[a].

Entry	Solvent	Time (h:min)	Yield (%)
1	CH_3CN	7:00	30
2	EtOH	7:00	92
3	MeOH	7:00	60
4	$CHCl_3$	7:00	Negligible
5	$EtOH/H_2O$ (1: 1)	7:00	30
6	H_2O	7:00	25
7	H_2O[b]	7:00	30
8	H_2O[c]	7:00	25
9	EtOH[b]	7:00	80
10	EtOH[c]	7:00	70

[a]All reactions were carried out with benzaldehyde (2 mmol), ethyl acetoacetate (2 mmol), urea (3 mmol), $Al(NO_3)_3{\cdot}9H_2O$ (0.3 mmol); [b]catalyst: $Al(NO_3)_3{\cdot}9H_2O$/SDS (1: 3) (15% mol); [c]catalyst: $Al(DS)_3$ (0.3 mmol).

(2 mmol, 210 mg), benzaldehyde (2 mmol, 212 mg), urea (3 mmol, 180 mg), and $Al(NO_3)_3{\cdot}9H_2O$ (0.3 mmol, 112 mg) in 95% ethanol (5 mL) was heated under reflux for 7 h. On cooling, the product crystallized from the solution. The pure solid, 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one, (92%, 479 mg, mp 202–204°C) was filtered, washed with cold ethanol (3 × 5 mL), and dried under vacuum.

2.3. Typical Reaction for the Synthesis of Biginelli Compounds in Solvent-Free Conditions. A mixture of ethyl acetoacetate (2 mmol, 210 mg), benzaldehyde (2 mmol, 212 mg), urea (3 mmol, 180 mg), and $Al(NO_3)_3{\cdot}9H_2O$ (0.3 mmol, 112 mg) was heated under solvent-free conditions for 30 min at 80°C. After completion of reaction, hot ethanol (5 mL) added to reaction mixture. On cooling, the product spontaneously crystallized from the solution. The pure solid, 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one, (97%, 505 mg, mp 202–204°C) was filtered, washed with cold ethanol (3 × 5 mL) and dried under vacuum.

Table 3: Influence of temperature on the solvent-free synthesis of ethyl-6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate in the presence of $Al(NO_3)_3{\cdot}9H_2O$[a].

Entry	Temperature (°C)	Time (min)	Yield (%)
1	r.t.	300	53
2	40	210	65
3	60	150	76
4	80	30	97

[a]All reactions were carried out with benzaldehyde (2 mmol), ethyl acetoacetate (2 mmol), urea (3 mmol), and $Al(NO_3)_3{\cdot}9H_2O$ (0.3 mmol).

3. Results and Discussion

In continuation of our work on the development of useful synthetic methodologies [23–25], we have observed that aluminum nitrate is an effective catalyst for the synthesis of Biginelli compounds (Figure 1). As a model reaction, we started to study the three-component aluminum nitrate catalyzed Biginelli condensation by examining the conditions required for the reaction involving benzaldehyde, urea, and ethyl acetoacetate to afford the corresponding 3,4-dihydropyrimidinone in refluxing ethanol.

Initially, we turned our attention toward screening appropriate concentration of aluminum nitrate (Table 1). In the first stage, we carried out the model reaction in absence of any catalyst (entry 1, Table 1) for which the yield of product was negligible. Afterward, we selected 5 mol% aluminum nitrate to catalyze the model reaction and found that the desired 3,4-dihydropyridinone was obtained in 70% yield. The reaction worked well when the amount of $Al(NO_3)_3{\cdot}9H_2O$ was increased from 10 to 15 mol%, but 15 mol% of $Al(NO_3)_3{\cdot}9H_2O$ gave highest yield, and larger

Table 4: Synthesis of various dihydropyrimidinones catalyzed by Al $(NO_3)_3 \cdot 9H_2O$ in refluxing ethanol (I) and solvent-free conditions at 80°C (II)[a].

Entry	R	R_1	X	Time (h:min.)		Yield (%)	
				I	II	I	II
1	Ph	OEt	O	7:00	00:30	92	97
2	Ph	OMe	O	7:00	00:20	93	95
3	Ph	OEt	S	8:00	00:60	80	85
4	4-Cl-C_6H_4	OEt	O	7:00	1:30	85	88
5	4-Cl-C_6H_4	OMe	O	7:00	1:30	80	90
6	2-Cl-C_6H_4	OEt	O	7:00	00:30	70	95
7	2-Cl-C_6H_4	OMe	O	7:00	00:30	80	97
8	4-CH_3-C_6H_4	OEt	S	6:00	2:00	90	95
9	2-MeO-C_6H_4	OEt	O	6:00	2:00	99	99
10	4-MeO-C_6H_4	OEt	O	7:00	3:00	88	92
11	3,4-DiMeO-C_6H_4	OMe	O	7:00	3:00	70	92
12	3-Br-C_6H_4	OEt	O	8:00	3:00	80	87
13	4-F-C_6H_4	OEt	O	9:00	2:30	85	99
14	2-Furyl	OMe	O	8:00	2:00	85	88
15	3-EtO-4-HO-C_6H_4	OEt	O	9:00	1:30	82	88
16	4-Me_2N-C_6H_4	OEt	O	8:00	3:00	80	92
17	3-O_2N-C_6H_4	OEt	O	9:00	3:00	70	90

[a]Yields refer to isolated products which were characterized by comparison of their spectroscopic and physical data with those of samples synthesized by reported procedures.

Table 5: Biginelli synthesis of 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one: Al$(NO_3)_3 \cdot 9H_2O$ in comparison with some recent reports.

Entry	Conditions	Time (h:min)	Yield (%)
1	Al$(NO_3)_3 \cdot 9H_2O$/SF, 80°C	00:15	98
2	Sulfated tungstate/SF, 80°C [28]	1:00	92
3	Silica gel-supported polyphosphoric acid (PPA-SiO_2)/CH_3CN, reflux [29]	1:00	88
4	$FeCl_3$ immobilized in Al-MCM 41/CH_3CN, reflux [30]	4:00	85
5	[Hmim]HSO_4/solvent-free, 110°C [31]	0:20	92
6	Alpha-zirconium sulfophenylphosphonate/SF, 80°C [32]	18:00	89
7	1,3-Dichloro-5,5-dimethylhydantoin/CH_3CN, reflux [22]	4:00	89

amount of catalyst did not improve the yields to a greater extent.

After investigation of the influence of catalyst amount on the yield of the reaction, various solvents including CH_3CN, EtOH, MeOH, Acetone, $CHCl_3$, EtOH/H_2O (1 : 1), and H_2O were tested and compared with solvent-free conditions (Table 2). As can be seen in Table 2, among the different solvents, ethanol gave the highest yield (Table 2, entry 2), whereas water did not yield good results in aluminum nitrate-catalyzed Biginelli reaction (Table 2, entry 7). Also, addition of catalytic amount of sodium dodecyl sulfate (SDS) only improved yield of product up to 5%. In addition, we prepared $Al(DS)_3$ by reaction of aluminum nitrate with SDS according to reported procedure [26] and used it as catalyst in the model reaction in water as solvent under the reflux condition, but $Al(DS)_3$ did not improve yield of reaction in our hand. We finally identified ethanol as the most efficient solvent for aluminum nitrate-catalyzed Biginelli reaction. To investigate the versatility as well as the capacity of our method, the reactions were examined in solvent-free conditions.

In solvent-free conditions, the yield increased, and the reaction time decreased (Table 2, entry 12). In addition, at low temperature and long reaction times only smaller amounts of the desired products were obtained (Table 3, entry 1).

After optimizing the reaction conditions, various aromatic aldehydes carrying either electron-releasing or electron-withdrawing substituents in the ortho, meta, and para positions afforded good to excellent yields of the products both in refluxing ethanol and solvent-free conditions. An important feature of this procedure is that despite the high oxidizing potential of aluminum nitrate, functional groups such as ethers and hydroxy survive under the reaction conditions. Thiourea was used with similar success to provide the corresponding 3,4-dihydropyrimidin-2(1*H*)-thiones which are also of interest with regard to their biological activities (Table 4, entries 3, 8) [27].

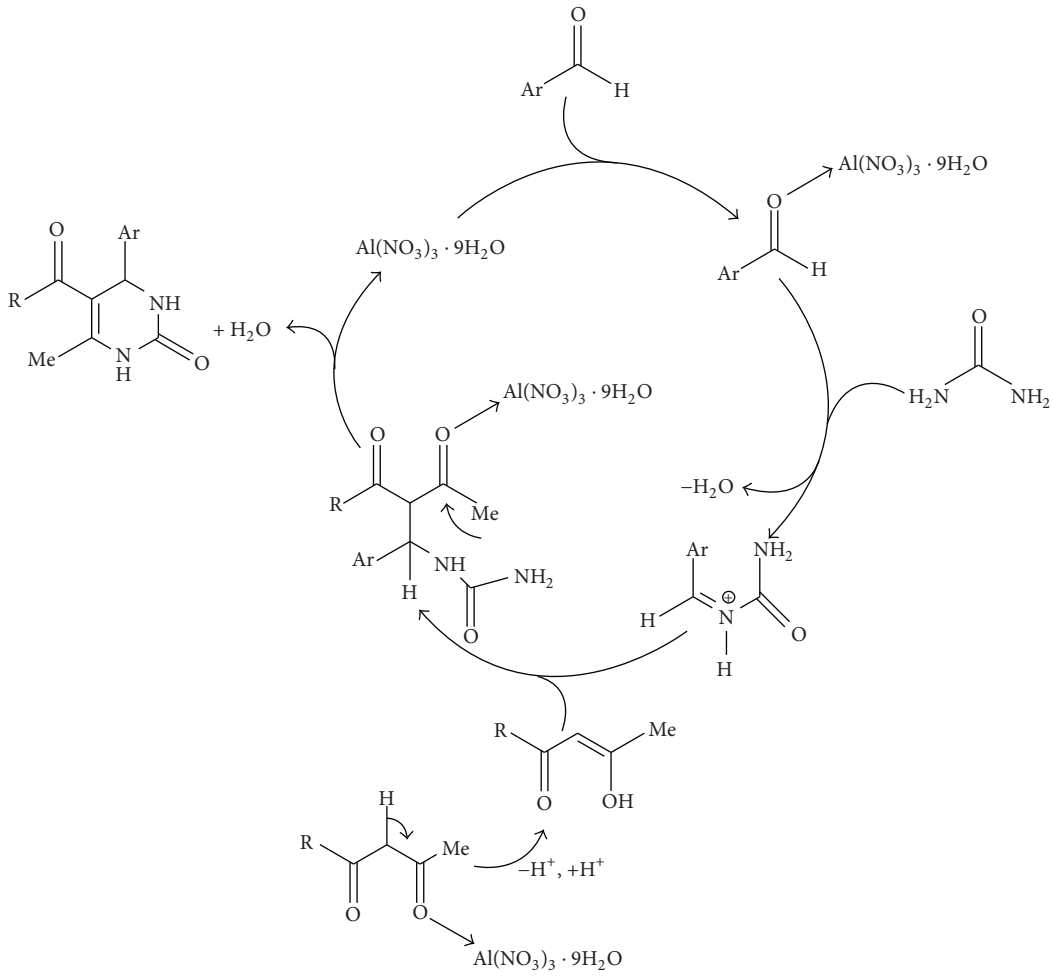

Figure 2: Proposed mechanism for the aluminum nitrate-catalyzed Biginelli reaction.

We can reach a better conclusion by comparing the performance of the present work with some other recent reports available in the literature, as illustrated in Table 5.

The mechanism of Biginelli reaction has been investigated thoroughly [33]. According to Kappe [34], the first step in the mechanism is believed to be the condensation between the aldehyde and urea. The iminium intermediate generated acts as an electrophile for the nucleophilic addition of the ketoester enol, and the ketone carbonyl of the resulting adduct undergoes condensation with the urea NH_2 to give the cyclized product (Figure 2).

4. Conclusions

In conclusion, the present procedure provides an efficient and improved modification of the Biginelli reaction. Mild reaction conditions, operational simplicity and easy work-up, good to excellent yields, cheap and nontoxic catalyst, and short reaction times (in solvent-free conditions) are features of this new procedure.

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