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One-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones using lanthanum chloride as a catalyst

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Abstract

An efficient synthesis of 3,4-dihydropyrimidinones using lanthanum chloride heptahydrate as a catalyst from an aldehyde, β-keto ester and urea or thiourea in ethanol is described. Compared to the classical Biginelli reaction conditions, this new method consistently has the advantage of good yields (56–97%).

Keywords: Biginelli reaction; dihydropyrimidinones; lanthanum chloride heptahydrate; one-pot condensation; synthesis.

During recent years, the use of lanthanide(III) compounds as catalysts or promoters in organic synthesis has attracted great interest from many chemists.[1] Lanthanide additives or complexes can enhance the reactivity and selectivity of many types of reaction, such as reduction, carbon–carbon bond formation, aldol condensation, cycloaddition, ring-opening and polymerization.

The Biginelli reaction was first reported more than a century ago and recently reviewed,[2] and involves the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones of type **4** by a very simple one-pot condensation reaction of ethyl acetoacetate **1**, benzaldehyde **2** and urea **3** in ethanol. However, this one-pot, one-step protocol often provides only low to moderate yields of the desired target molecules **4** (Scheme 1), in particular when substituted aromatic or aliphatic aldehydes are employed.

In the past decade, dihydropyrimidine derivatives have exhibited important pharmacological properties, e.g. as the integral backbones of several calcium channel blockers, antihypertensive agents, alpha-1a-antagonists, and neuropeptide Y (NPY) antagonists.[3] Therefore, the discovery of milder and practical routes for the synthesis of dihydropyrimidin-2(1*H*)-ones by the Biginelli reaction continues to attract the attention of researchers. Several improved procedures for the preparation of DHPMs ('Biginelli compounds') have recently been reported, either by modifica-

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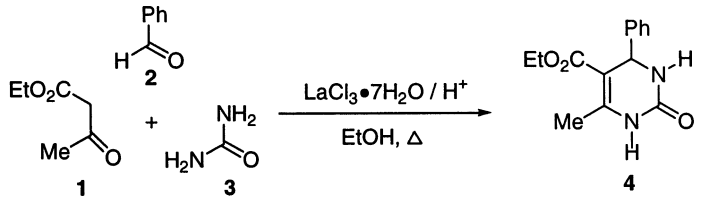
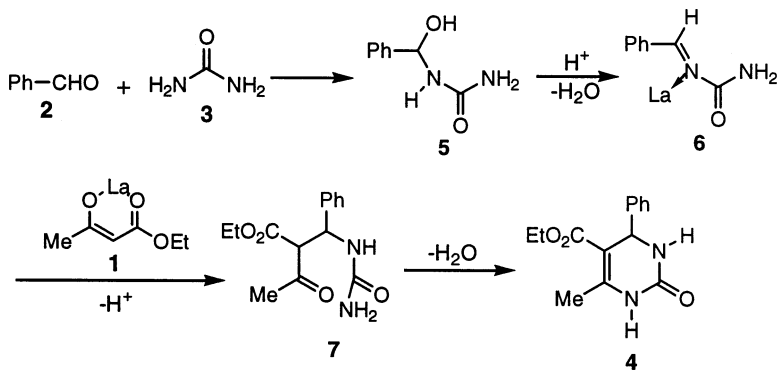


Scheme 1.

tion of the classical one-pot Biginelli approach itself,[4–8] or by the development of novel, but more complex multistep strategies.[9] In addition, several combinatorial approaches towards DHPMs **4** have been advanced using solid-phase or fluorous phase reaction conditions.[10]

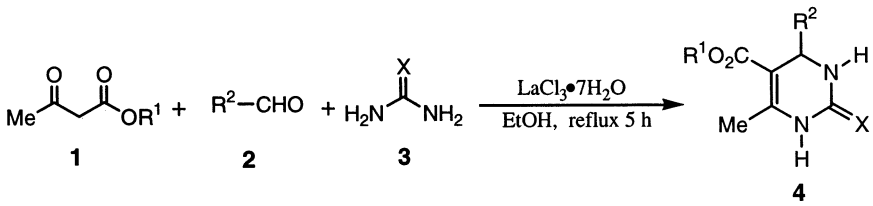
Here we wish to report our preliminary investigation concerning the direct synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones. In this paper, we describe a general and practical route for the Biginelli cyclocondensation reaction using lanthanum chloride heptahydrate as the catalyst (Method A).[11] This is a novel, one-pot combination that not only preserves the simplicity of Biginelli's one-pot reaction but also consistently produces excellent yields of the dihydropyrimidin-2(1*H*)-ones. In the presence of the $LaCl_3 \cdot 7H_2O$ (5 mmol), the reaction of β-keto ester **1** (10 mmol), aldehyde **2** (10 mmol), and urea or thiourea **3** (15 mmol) was carried out in a one-pot condensation employing refluxing EtOH, which has previously been employed successfully in the Biginelli condensation as solvent. After the reaction was completed, the dihydropyrimidinones **4a**–**t** precipitated from the reaction mixture. Even for aliphatic aldehydes (i.e. butyraldehyde and *iso*-butyraldehyde), which normally show extremely poor yields in the Biginelli reaction,[12] 60 and 56% yields of the corresponding dihydropyrimidin-2(1*H*)-ones **4j** and **4k** could be obtained (Table 1).

Recently, the mechanism of the Biginelli reaction was reinvestigated in detail by Kappe.[16] He proposed and established that the first step in this reaction, the acid-catalyzed formation of an acyl imine intermediate formed by reaction of the aldehyde with urea, is the key rate-limiting step. Interception of the iminium ion by ethyl acetoacetate produces an open-chain ureide **7** which subsequently cyclizes to the dihydropyrimidinones **4**. Because of the **4f** empty orbital in the lanthanum ion, a complex **6** can be formed through a coordinative bond and stabilized by lanthanum. So we propose a mechanism for the lanthanum promoted Biginelli reaction as follows (Scheme 2):



Scheme 2.

Table 1
DHPMs **4** synthesized using $LaCl_3 \cdot 7H_2O$ versus classical Biginellis' conditions



DHPM	X	R^1	R^2	Yield (%)	
				A[a]	B[b]
4a	O	Et	C_6H_5	95	78[13]
4b	O	Et	4-(CH_3O)-C_6H_4	93	61[13]
4c	O	Et	3,4-(OCH_2O)-C_6H_3	91	49[13]
4d	O	Et	4-(OH)-3-(CH_3O)-C_6H_3	92	43[13]
4e	O	Et	4-(OH)-C_6H_4	89	67[13]
4f	O	Et	4-(NO_2)-C_6H_4	80	58[13]
4g	O	Et	4-(Cl)-C_6H_4	92	56[4]
4h	O	Et	3-(Cl)-C_6H_4	87	56[8]
4i	O	Et	3-(Br)-C_6H_4	97	58[8]
4j	O	Et	$CH_3CH_2CH_2$	60	15[12]
4k	O	Et	$(CH_3)_2CH$	56	10[12]
4l	O	Et	2-(OH)-C_6H_4	76	19[13]
4m	O	Et	Furyl-	67	36[13]
4n	O	Et	2,4-$(Cl)_2$-C_6H_3	93	69[c]
4o	O	Me	C_6H_5	97	42[4]
4p	O	Me	4-(CH_3O)-C_6H_4	82	28[4]
4q	O	Me	4-(Cl)-C_6H_4	96	56[4]
4r	O	Me	4-(NO_2)-C_6H_4	68	41[4]
4s	S	Et	C_6H_5	96	70,[14] 42[13]
4t	S	Et	4-(CH_3O)-C_6H_4	85	80[14]

[a] Method A: new reaction conditions (cat. $LaCl_3 \cdot 7H_2O$/HCl in EtOH, reflux 5 h).[11]
[b] Method B: classical Biginelli conditions (cat. HCl in EtOH reflux 18 h).[13–15]
[c] This work.

In conclusion, we have developed a simple and efficient method for the direct preparation of substituted dihydropyrimidinones using lanthanum chloride heptahydrate as a catalyst in good yields from readily available starting materials.

Acknowledgements

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11. *General procedure for $LaCl_3 \cdot 7H_2O$—mediated preparation of pyrimidines* ***4***: a solution of β-keto ester (**1**, 10 mmol), the appropriate aldehyde (**2**, 10 mmol), urea or thiourea (**3**, 15 mmol), $LaCl_3 \cdot 7H_2O$ (1.85 g, 5 mmol) and conc. HCl (1–2 drops) in EtOH (20 mL) was heated under reflux for 5 h. After cooling, the reaction mixture was poured onto 50 g of crushed ice. Stirring was continued for several minutes; the solid products were filtered, washed with cold water (2×50 mL) and a mixture (1:1) of ethanol–water (2×20 mL) and subsequently dried. All the products (except **4n**) are known compounds which were characterized by IR and ^{1}H NMR spectral data and their mps compared with literature reported mps. Data for **4n**: mp 248–250°C. IR (KBr): 3219, 3104, 2969, 1699, 1641 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz): 9.33 (br s, N1-*H*), 7.77 (br s, N3-*H*), 7.31–7.57 (m, Ar-*H*), 5.60 (s, C4-*H*), 3.90 (q, OCH_2CH_3, J=7.2 Hz), 2.29 (s, C6-CH_3), 1.02 (t, OCH_2CH_3, J=7.2 Hz). MS m/e 328 (M^+, 6.69), 330 (M^++2, 4.10), 299 (47.18), 293 (68.72), 255 (40.00), 183 (100.00), 155 (32.82), 137 (25.64). Anal. calcd for $C_{14}H_{14}Cl_2N_2O_3$: C, 51.06; H, 4.26; N, 8.51. Found: C, 51.32; H, 4.43; N, 8.24.
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