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Efficient synthesis of pyrimidinone derivatives by ytterbium chloride catalyzed Biginelli-type reaction under solvent-free conditions

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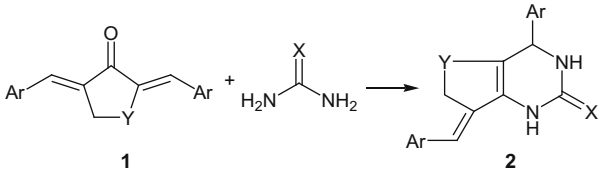
ABSTRACT

An efficient and clean method was developed for the one-pot synthesis of pyrimidinones by ytterbium chloride catalyzed Biginelli-type reaction of aromatic aldehyde, cyclopentanone, and urea or thiourea under solvent-free conditions.

Pyrimidinone skeleton exists in many natural or synthetic biologically active materials, and its derivatives are applied in various pharmaceutical and biochemical fields.[1,2] It is of great interest that specifically functionalized pyrimidinone may possess specific biological properties. For example, it was recently found that some fused pyrimidinones **2** carrying an arylidene moiety (Scheme 1) are potential antitumor agents based on sufficient antitumor screening data.[3] Some of these analogues also showed, besides the broad-spectrum antitumor activity, a distinctive pattern of selectivity toward individual cell line such as that of leukemia. These findings make it highly necessary to develop efficient methods for the synthesis of this type of pyrimidinones. According to the previous literature, these arylidene heterobicyclic pyrimidinones were typically synthesized by the reaction of α,α′-bis(arylidene)cycloalkanones with urea or thiourea (Scheme 1). In most cases, strong Bronsted acid[4] such as HCl, or base[3,5] such as sodium alkoxide and potassium hydroxide was a necessary requirement for the smooth reaction. More recently, Pan[6] described an efficient alternative for the synthesis of these fused pyrimidinones by a three-component condensation with aromatic aldehyde, cyclopentanone, and urea or thiourea as starting materials, which was supposed to be a Biginelli-type reaction. However, the use of stoichiometric amounts of TMSCl as additional reagent and mixed DMF/CH_3CN as reaction solvent appeared to be necessary to obtain satisfactory results.

Metal-catalyzed reactions[7] are recognized as attractive and environmentally benign methods in synthetic chemistry with regard to the development of green chemistry. In this area, notable progress has been made in the applications of lanthanide reagents as catalysts in organic synthesis in recent years.[8] Lanthanides are nontoxic and relatively abundant in nature, and the success in developing many useful reactions efficiently catalyzed by lanthanide compounds is attributed to the unique features of lanthanide centers such as the high electrophilicity, variable metal ion radius, and tunable coordination patterns. Our interest in this area has led us to explore the lanthanide compounds effective in the synthesis of a series of biologically active materials including α-amino phosphonates, quinolines, and pyrimidines.[9] Herein, this letter attempts to describe the catalytic activity of lanthanide chloride ($LnCl_3$) in the one-pot synthesis of pyrimidinone from aromatic aldehyde, cyclopentanone, and urea or thiourea, the so-called Biginelli-type three-component reaction.

Previous work has demonstrated that samarium diiodide (SmI_2) can effectively catalyze the classical Biginelli reaction of aldehydes,



1 2

X = O, S

Y = $-CH_2-$, $-CH_2CH_2-$, $-N(CH_3)-CH_2-$

Scheme 1.

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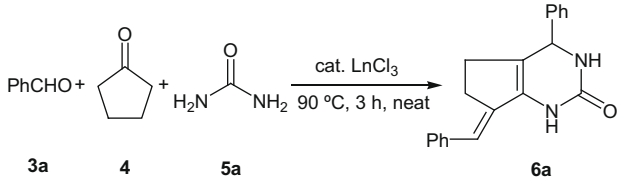
urea, and β-dicarbonyl compounds affording pyrimidinones in moderate to excellent yields.[9c] However, we failed to achieve the Biginelli-type three-component condensation of aldehyde, cycloalkanone, and urea with SmI_2 as catalyst, and none of the expected arylidene heterobicyclic pyrimidinone was detected. Surprisingly, when the reaction was conducted in the presence of catalytic amount of ytterbium chloride ($YbCl_3$), a readily available and economical lanthanide Lewis acid, a satisfying result was obtained. This encouraged us to examine the catalytic activity of a series of lanthanide chlorides in the condensation of benzaldehyde, cyclopentanone with urea, as a model reaction, at 90 °C under solvent-free condition. As shown in Table 1, all the lanthanide chlorides screened were effective in catalyzing the reaction, and the influence of central metal on the activity was observed. The active sequence is Yb > Er ≈ Y ≈ Gd ≈ Sm > Nd ≈ La, which is in contrast to the order of their ionic radius. $YbCl_3$ was then chosen as a representative lanthanide source for the investigation on catalyst loading. When the loading of $YbCl_3$ was increased from 1 mol % to 10 mol % (entries 7–10), the yield of pyrimidinone first increased until to a maximum and then gradually decreased, and the highest yield was obtained at 3 mol % of catalyst loading (entry 8). The analysis of the crude product indicated that overused catalyst may lead to undesired side reactions.

To our delight, this Lewis acid-catalyzed reaction was carried out under a mild, simple, and clean condition. First, no solvent is required during the reaction stage, which not only avoids the use of auxiliary reagents that may be toxic or flammable, but also simplifies the follow-up operation, and the purifications of the products are performed simply by filtration and washing. Second, the reaction works well while being exposed to air, so the steps of drying and protection, which is usually essential for most of the reactions that lanthanide compounds participate in, are eliminated. Thus, this procedure provides an efficient, convenient, and environmentally friendly protocol for the synthesis of pyrimidinones.

Further optimization of the reaction conditions was attempted. The results are summarized in Table 2. The influence of temperature was examined for the model reaction first. Raising the reaction temperature from 60 °C to 90 °C (entries 1–3) led to an increase in yield from 43% to 79%, while the temperature over 100 °C (entries 4–5) resulted in a decrease in yield. Then the effect of reaction time on yield (entries 3 and 6–9) was investigated and the highest yield was obtained after 3 h. The results showed that lower temperature and shorter reaction time may result in incomplete reaction while overheating and excessively prolonged time lead to complicated side reactions.

It is worth mentioning that although the product **6a** is actually condensed by benzaldehyde, cyclopentanone, and urea at a 2:1:1 ratio, the reaction at this ratio of substrate gave the yield lower than that obtained at a 1:1:1.2 ratio (entries 3 and 9). This means that excessively used cyclopentanone and urea played important roles in promoting the conversion of benzaldehyde to the product. Corresponding contrastive reactions were performed and the results indicated that whichever of the cyclopentanone or urea was used at double the equivalent, respectively, the yields were appreciably improved (entries 10 and 12). Further excessive cyclopentanone or urea still affected the yield in the positive direction (entries 11 and 13), but the results obtained in all these attempts could not reach that in the case cyclopentanone and urea were used at the double equivalent at the same time. The reason for this is not yet clear.

Table 1
$LnCl_3$ catalyzed one-pot synthesis of pyrimidinone **6a**[a]



3a 4 5a 6a

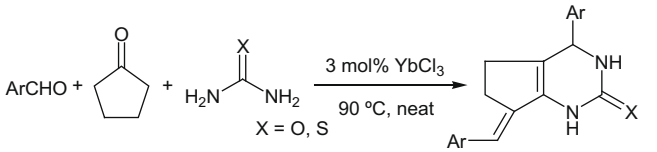
Entry	Catalyst	Loading (mol %)	Yield (%)
1	$LaCl_3$	3	62
2	$NdCl_3$	3	62
3	$SmCl_3$	3	71
4	$GdCl_3$	3	71
5	YCl_3	3	72
6	$ErCl_3$	3	72
7	$YbCl_3$	1	52
8	$YbCl_3$	3	79
9	$YbCl_3$	5	71
10	$YbCl_3$	10	63

[a] Typical reaction conditions: aldehyde/cyclopentanone/urea = 1:1:1.2, 90 °C, 3 h.

Table 2
Effects of temperature, time, and ratio of substrates on the synthetic reaction of **6a**

Entry	Temp. (°C)	Time (h)	**3a**:**4**:**5a**	Yield (%)
1	60	3	1:1:1.2	43
2	80	3	1:1:1.2	68
3	90	3	1:1:1.2	79
4	100	3	1:1:1.2	79
5	120	3	1:1:1.2	74
6	90	2	1:1:1.2	65
7	90	6	1:1:1.2	69
8	90	10	1:1:1.2	62
9	90	3	2:1:1.2	43
10	90	3	2:1:2.4	55
11	90	3	2:1:3.6	70
12	90	3	2:2:1.2	71
13	90	3	2:3:1.2	78

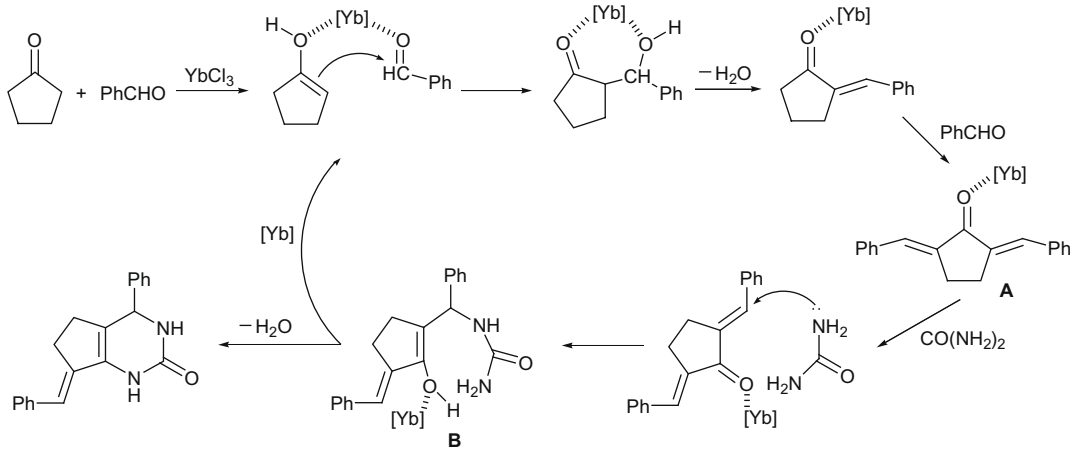
Table 3
$YbCl_3$-catalyzed one-pot synthesis of pyrimidinone **6**[a]



3 4 5 6

Entry	Ar	X	Time (h)	Product	Yield (%)
1	Ph	O	3	**6a**	79
2	1-naphthyl	O	5	**6b**	81
3	*p*-CH_3Ph	O	5	**6c**	70
4	*o*-CH_3Ph	O	5	**6d**	51
5	*p*-CH_3OPh	O	5	**6e**	69
6	*m*-CH_3OPh	O	5	**6f**	71
7	*o*-CH_3OPh	O	5	**6g**	60
8	*p*-BrPh	O	4	**6h**	74
9	*p*-ClPh	O	3	**6i**	75
10	*m*-ClPh	O	3	**6j**	71
11	*o*-ClPh	O	3	**6k**	55
12	*p*-FPh	O	3	**6l**	91
13	*m*-FPh	O	3	**6m**	61
14	*o*-FPh	O	3	**6n**	64
15	*p*-CNPh	O	5	**6o**	90
16	*p*-NO_2Ph	O	5	**6p**	89
17	*m*-NO_2Ph	O	5	**6q**	50
18	Ph	S	10	**6r**	90 (74)[b]
19	*p*-ClPh	S	10	**6s**	82
20	*p*-FPh	S	8	**6t**	92
21	*p*-CH_3Ph	S	12	**6u**	59

[a] Typical reaction conditions: aldehyde/cyclopentanone/urea or thiourea = 1:1:1.2, 3 mol % $YbCl_3$ relative to aldehyde, 90 °C.
[b] The reaction was run for 3 h.



Scheme 2.

In order to examine the scope and generality of this procedure, we extended the methodology to different aromatic aldehydes. The results are presented in Table 3. All the reactions, consisting of those involving *ortho*-, *meta*-, and *para*-substituted benzaldehydes, proceeded smoothly and afforded the corresponding benzylidene heterobicyclic pyrimidinones in moderate to high yields. Electronic effects can be observed. The electron-donating group(EDG)-substituted benzaldehydes (*para*-substituted, entries 3 and 5) required prolonged reaction time to give the yields close to those of weaker electron-withdrawing group(EWG)-substituted ones (entries 8 and 9), while stronger EWG-substituted ones (entries 12, 15, and 16) gave evidently increasing yields. *ortho*-Substituted benzaldehydes (entries 4, 7, 11, and 14), whether the substituent is EDG or EWG, afforded the corresponding pyrimidinones in relatively lower yields, indicating an obvious steric effect. Thiourea exhibited behavior similar to that of urea.

The mechanism of the Biginelli reaction established by Kappe[10] proposed that the key step in this cyclocondensation process should involve the formation of an *N*-acyliminium ion intermediate or a Lewis acid stabilized imine intermediate from the aldehyde and urea precursors under acid-catalyzed conditions. However, the byproduct isolated from the crude product of our model reaction, which was detected as α,α′-dibenzylidene cyclopentanone **A** and should be produced from benzaldehyde and cyclopentanone, suggests another hypothesis. The first step of the present reaction is probably a Lewis acid-catalyzed cross-aldol condensation of aldehyde with ketone to produce **A**, which is similar to the $Yb(OTf)_3$-catalyzed same reaction described by Wang.[11] Then the Michael addition of urea to **A** leads to ureide **B**, which subsequently eliminates water and cyclizes to form pyrimidinone (Scheme 2).

In conclusion, we describe here an efficient method for the synthesis of fused pyrimidinone by $YbCl_3$-catalyzed Biginelli-type reaction of aromatic aldehyde, cyclopentanone, and urea or thiourea under solvent-free conditions. The reaction presented here has several advantages: it is clean, one-pot, and can be handled easily. These environmentally friendly features make the catalytic procedure a practically and environmentally acceptable method for the synthesis of pyrimidinones.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.103.

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