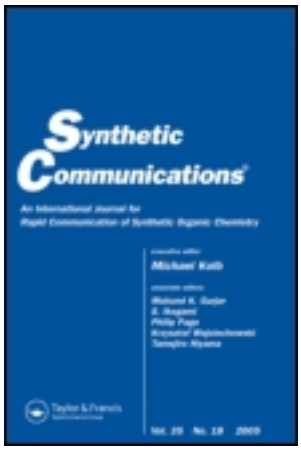

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Lanthanide Triflate Catalyzed One-Pot Synthesis of Dihydropyrimidin-2(1*H*)-thiones by a Three-Component of 1,3-Dicarbonyl Compounds, Aldehydes, and Thiourea Using a Solvent-Free Biginelli Condensation

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ABSTRACT

Novel one-pot Biginelli-type reaction has been developed. Aromatic and aliphatic aldehydes with β-dicarbonyl compounds and thiourea

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in the presence of catalytic amount 5 mol% of $Yb(OTf)_3$ at 100° C for 60–90 min under solvent-free conditions proceeded smoothly to afford corresponding dihydropyrimidin-thiones. The yields of the classical Biginelli reaction can be increased from 20–50% to 81–91% while the reaction time was shortened from 18–48 h to 60–90 min. In addition the catalyst can be easily recovered and reused.

Key Words: Lanthanide triflate; Biginelli reaction; One-pot synthesis; Dihydropyrimidin-2(1H)-thiones.

INTRODUCTION

In the recent years, the synthesis of Dihydropyrimidinones has received an increasing amount of attention because their derivatives are pharmacologically important as calcium channel blockers, antihypertensive agents, and $alpha_1$-1-a-antagonists.[1] Furthermore, several marine alkaloids with interesting biological activities containing the dihydropyrimidin-5-carboxylate unit have been isolated.[2] Thus, synthetic methods for preparing this heterocyclic nucleus have been developed.[3] In 1893 pietro Biginelli firstly reported the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones by a very simple one-pot condensation reaction of benzaldehyde, ethyl acetoacetate, and urea under strongly acidic conditions,[4] unfortunately, one serious drawback of this Biginelli reaction is low yields (20–50%), when using substituted aromatic, aliphatic aldehydes, in particular using thioureas.[5] Thus, Biginelli reaction for the synthesis of DHPMs (''Bignelli: Compounds,'' DHPMs) has received renewed interest and several improved procedures have recently been reported,[6] either by modification of the classical one-pot Biginelli approach itself[7] or by the development of novel, but more complex multi-step strategies[8] was reported that these methods involve strong Lewis acids such as BF_3,[9] Protic acids such as HCl[10] and other milder Lewis acid such as $InCl_3$,[11] $BiCl_3$,[12] Ferric and Nickel Chloride hexahydrates,[13] the acid clay montmorillonite KSF,[14] Zeolite,[15] solid-supported ytterbium(III) reagent.[16] The reported Biginell's reactions normally require prolonged reaction time and using organic solvent.

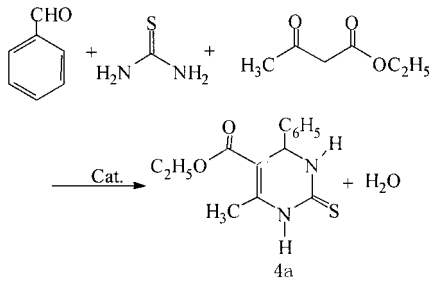
The use of lanthanide compounds, especially lanthanide triflates Lewis acid as catalysts in organic synthesis has attracted great interest from many chemists.[17] We have recently reported a series of lanthanide triflates Lewis acid catalyzed organic reaction, such as ytterbium

catalyzed ee reaction,[18] scandium triflate catalyzed [2 + 2] cycloaddition reaction,[19] one-pot synthesis of amino phosponate,[20] asymmetric glyoxylate-ene reaction catalyzed by C_2-symmtric chiral *bis*(oxazoline)-lanthanide triflates complexes.[21]

Continuing our recent work in lanthanide triflate catalyzed Biginelli reaction: one-pot synthesis of dihydropyrimidin under the solvent-free condition,[22] we have focused our attention on the lanthanide triflate catalyzed synthesis of the dihydropyrimidin-2(1*H*)-thiones. We wish to report here a novel lanthanide triflate catalyzed Biginelli reaction, applied to one-pot synthesis of dihydropyrimidin-2(1*H*)-thiones by a three component of thiourea, 1,3-dicarbonyl compounds, aldehyde under solvent-free condition to, which not only is very simple and excellent-yielding (81–91%) but also greatly development environmentally friendly and effective synthetic methods.

RESULTS AND DISCUSSION

For the present study we have selected benzaldehyde, ethyl acetoacetate, and thiourea as model compounds using lanthanide triflate as a catalyst and have tested a variety of reaction conditions (Sch. 1). It was found that, in the presence of 0.05 equiv. of a lanthanide triflate, the modification one-pot reaction of the classical Biginelli under solvent-free can proceed smoothly to afford the corresponding dihydropyrimidin-2(1*H*)-thiones in excellent yields. The reaction results are summarized in Table 1. We investigated the effectiveness of three lanthanide triflate, $Yb(OTf)_3$, $La(OTf)_3$, and $La(OTf)_3$ in catalyzing the reaction and compared with the reaction using several Lewis acids. There was no significant difference among the three lanthanide triflates in terms of the



Scheme 1.

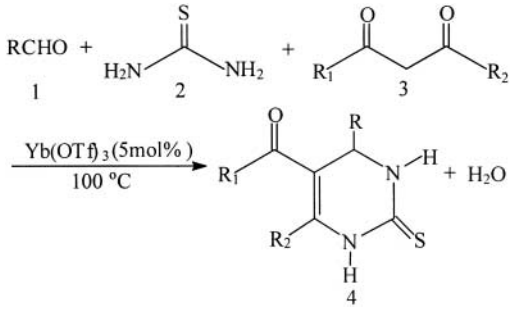
Table 1. Reaction of benzaldehyde, ethyl acetoacetate, and thioureas under different reaction conditions.

Entry	Solvent[a]	Catalyst	Amount of catalyst (mol%)	Yield (%)[d]
1	H_2O	$Yb(OTf)_3$	5	18
2	Toluene	$Yb(OTf)_3$	5	80
3	$HOCH_2CH_2OCH_3$	$Yb(OTf)_3$	5	85
4	CH_2Cl_2	$Yb(OTf)_3$	5	16
5	THF	$Yb(OTf)_3$	5	34
6	None[b]	$Yb(OTf)_3$	5	92
7	None	$Yb(OTf)_3$	20	91
8	None	$Yb(OTf)_3$	10	91
9	None	$Yb(OTf)_3$	2.5	88
10	None	$Yb(OTf)_3$	1.5	78
11	None	$Sc(OTf)_3$	5	89
12	None	$La(OTf)_3$	5	86
13	None	$LaCl_3$	5	40
14	None	$ScCl_3$	5	43
15	None	$YbCl_3$	5	46
16	None	$ZnCl_2$	5	5
17	None	$SnCl_2$	5	6
18	None	$Yb(OTf)_3$[c]	5	89, 87, 84

[a]Refluxed for 6 h; [b]100°C for 60 min; [c]Catalyst was reused in three times; [d]Isolated yield.

yield, but $Yb(OTf)_3$ showed particularly superior catalytic activity and could be reused three times and exhibited the same catalytic activity (the yields of **4a**: first: 89%, second: 87%, third: 84%). Use of just 5 mol% of $Yb(OTf)_3$ is sufficient to push the reaction forward. Higher amount of $Yb(OTf)_3$ did not improve the result to a great extent. Some lanthanide compounds such as $YbCl_3$, $ScCl_3$, and $LaCl_3$ gave low yields (46%, 43%, and 40%) at the first use. In contrast, the other Lewis acids such as $ZnCl_2$ and $SnCl_2$ gave lower yields. Effect of solvents on the yields of dihydropyrimidin-2(1*H*)-thiones in the model reaction under the influence of a catalyst amount of Yb(OTf) (5 mol%) are shown in Table 1 too. $HOCH_2CH_2OCH_3$ was the best solvent among those tested, such as toluene (80%), THF (34%), Dichloromethane (16%), and water (18%). Reaction under solvent-free condition is especially appealing, the yields were significantly raised (92%), and the reaction time was shortened from 18 h to 60 min.

The reaction of several aromatic and aliphatic aldehydes, 1,3-dicarbonyl compounds and thiourea were examined in the presence of a catalytic amount (5 mol%) of $Yb(OTf)_3$ under solvent-free at 100°C for 60 min (Sch. 2) and the results are summarized in Table 2. In all cases, the one-pot reaction proceeded smoothly to afford the corresponding dihydropyrimidin-2(1*H*)-thiones in high yield. Aromatic aldehydes either electron-donating or electron-withdrawing provided excellent yields of products, and aliphatic aldehydes such as *n*-valeric and is butyric aldehyde afforded corresponding dihydropyrimidin products in 76% (**4j**) and 75% (**4i**) yield. Aromatic aldehydes have higher reactivity than aliphatic aldehydes. Similarly, an α,β-unsaturated aldehyde also give



Scheme 2.

Table 2. Ytterbium triflate catalyzed synthesis of different dihydropyrimidinones under the solventless conditions.

Entry	*R*	R_1	R_2	Product	Yield (%)
1	C_6H_5	C_2H_5O	CH_3	**4a**	92
2	4-(CH_3O)-C_6H_4	C_2H_5O	CH_3	**4b**	90
3	4-(NO_2)-C_6H_4	C_2H_5O	CH_3	**4c**	88
4	4-(Cl)-C_6H_4	C_2H_5O	CH_3	**4d**	89
5	2,4-$(Cl)_2$-C_6H_3	C_2H_5O	CH_3	**4e**	87
6	3-(NO_2)-C_6H_4	C_2H_5O	CH_3	**4f**	86
7	$C_6H_5CH{=}CH$	C_2H_5O	CH_3	**4g**	81
8	$C_6H_5CH_2CH_2$	C_2H_5O	CH_3	**4h**	80
9	*i*-Pr	C_2H_5O	CH_3	**4i**	75
10	*n*-Bu	C_2H_5O	CH_3	**4j**	76
11	C_6H_5	CH_3	CH_3	**4k**	85
12	C_6H_5	CH_3O	CH_3	**4l**	91

the product **4g** (81% yield). Compared to classical Biginelli method, one additional important feature of the present protocol is the ability to tolerate the variation in all the three components. Besides β-ketone ester, the β-diketone can also be employed.

We have recently investigated the mechanism[22] of the Biginelli reaction and proposed that it must first form an acyl imine intermediate, by the reaction of the aldehyde with thiourea and activated by lanthanide coordination which is the key and rate-limiting step, especially the S=C double bond by lanthanide is stabilized. Interception of the acyl imine by β-ketoester compound produces an open chain ureide, which subsequently cyclizes to that dihydropyrimidin-2(1*H*)-thiones.

In conclusion, ytterbium triflate $Yb(OTf)_3$ were found to be efficient catalyst in one-pot reaction of aldehydes, 1,3-dicarbonyl compounds, and thiourea to afford dihydropyrimidin-2(1*H*)-thiones in good for excellent yields under solvent-free condition. This report discloses a new and simple modification of the Biginelli's reaction. The yields of the one-pot Biginelli reaction can be increased from 20–50 to 81–91% while the reaction time was shortened from 18–48 h to 60–90 min. Other important feature of this Biginelli reaction is that the catalyst can be easily recovered from aqueous layer after the reaction is completed and can be reused with no less of yield. It not only led to economical automation, but also reduces hazardous pollution to achieve environmentally friendly processes and could replace traditional Lewis acid catalysis.

EXPERIMENTAL SECTION

General

Melting points were determined on a Kofler hot stage. ^{1}H NMR spectra were recorded at 300 MHz or 400 MHz in DMSO-d_6 using TMS as internal standard. ^{13}C NMR spectral measurements were performed at 75 MHz using DMSO-d_6 as an internal standard. IR spectra were obtained as KBr plates on FTS-185. Mass spectra were determined on a Finigan 8230 mass spectrometer.

Lanthanide triflate catalyzed synthesis of different dihydropyrimidin-2(1*H*)-thione under the solventless conditions: aldehyde (1 mmol), β-dicarbonyl compound (1 mmol), thiourea (1.5 mmol), and $Yb(OTf)_3$ (0.05 mmol, 5 mol%) were heated at 100°C, under stirring for 60–90 min. Then water was added and the product was extracted with ethyl acetate. After the organic layer was dried (Na_2SO_4) and

evaporated, the residue was recrystallized by ethyl acetate and hexane to products **4**.

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-thione (4a): M.p. 207–208°C; ^{1}H NMR: $\delta = 10.30$ (s, 1H, NH), 9.63 (s, 1H, NH), 7.28 (m, 5H, arom CH), 5.18 (s, 1H, CH), 4.00 (q, $J = 7.0$ Hz, 2H, OCH_2), 2.29 (s, 3H, CH_3), 1.10 (t, $J = 7.06$ Hz, 3H, OCH_2CH_3); ^{13}C NMR: $\delta = 12.2$, 15.5, 52.2, 57.8, 99.2, 124.7, 125.8, 126.6, 143.1, 163.4, 172.6; IR (KBr): 3243, 1711, 1627 cm^{-1}; MS (70 eV, EI): m/z (%): 276 (M, 60), 199 (100); Anal. calcd. for $C_{14}H_{16}N_2O_2S$: C, 60.85; H, 5.84; N, 10.14. Found: C, 60.81; H, 5.85; N, 10.11.

5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione (4b): M.p. 140–141°C; ^{1}H NMR: $\delta = 10.35$ (s, 1H, NH), 9.57 (s, 1H, NH), 7.13 (d, $J = 8.65$ Hz, 2H, arom CH), 6.90 (d, $J = 8.71$ Hz, 2H, arom CH), 5.12 (s, 1H, CH), 4.00 (q, $J = 7.07$ Hz, 2H, OCH_2), 3.72 (s, 3H, OCH_3), 2.29 (s, 3H, CH_3), 1.11 (t, $J = 7.08$ Hz, 3H, CH_3); ^{13}C NMR: $\delta = 14.0$, 17.9, 55.1, 55.3, 60.2, 103.0, 114.0, 127.9, 134.7, 142.7, 159.4, 165.3, 173.7; IR (KBr): 3244, 1707, 1634 cm^{-1}; MS (70 eV, EI): m/z (%): 306 (M, 48), 277 (100); Anal. calcd. for $C_{15}H_{18}N_2O_3S$: C, 58.80; H, 5.92; N, 9.14. Found: C, 58.78; H, 5.82; N, 9.04.

5-Ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2-(1*H*)-thione (4c): M.p. 208–209°C; ^{1}H NMR: $\delta = 10.50$ (s, 1H, NH), 8.28 (d, $J = 8.78$ Hz, 2H, arom CH), 9.78 (s, 1H, NH), 7.78 (d, $J = 8.70$ Hz, 2H, arom CH), 5.38 (d, $J = 3.2$ Hz, 1H, CH), 4.07 (q, $J = 7.6$ Hz, 2H, OCH_2), 2.35 (s, 3H, CH_3), 1.12 (t, $J = 7.5$ Hz, 3H, CH_3); IR (KBr): 3238, 2971, 1725, 1701, 1658, 1593 cm^{-1}; Anal. calcd. for $C_{14}H_{15}N_3O_4S$: C, 52.33; H, 4.71; N, 13.08. Found: C, 52.22; H, 4.61; N, 13.12.

4-(4-Chlorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione (4d): M.p. 209–210°C; ^{1}H NMR: $\delta = 10.58$ (s, 1H, NH), 9.75 (s, 1H, NH), 7.45 (d, $J = 0.8$ Hz, 2H, arom CH), 7.28 (d, $J = 8.6$ Hz, 2H, arom CH), 5.16 (s, 1H, CH), 4.02 (q, $J = 7.1$ Hz, 2H, OCH_2), 2.27 (s, 3H, CH_3), 1.12 (t, $J = 7.1$ Hz, 3H, CH_3); IR (KBr): 3242, 1705, 1638 cm^{-1}; Anal. calcd. for $C_{14}H_{15}N_2O_2ClS$: C, 54.10; H, 4.86; N, 9.01. Found: C, 54.08; H, 4.76; N, 9.03.

4-(2,4-Dichlorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)- thione (4e): M.p. 225–228°C; ^{1}H NMR: $\delta = 10.68$ (s, 1H, NH), 9.16 (s, 1H, NH), 7.67 (s, 1H, arom CH), 7.43 (d, $J = 8.1$ Hz, 1H, arom CH), 7.34 (d, $J = 8.2$ Hz, 1H, arom CH), 5.63 (s, 1H, CH), 3.96 (q, $J = 7.3$ Hz, 2H, OCH_2), 2.30 (s, 3H, CH_3), 1.01 (t, $J = 7.5$ Hz, 3H, CH_3); IR (KBr): 3359, 1695, 1624 cm^{-1}; Anal. calcd. for $C_{14}H_{14}N_2O_2Cl_2S$: C, 48.71; H, 4.09; N, 8.11. Found: C, 48.69; H, 4.05; N, 8.08.

5-Ethoxycarbonyl-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2-(1*H*)-thione (4f): M.p. 206–207°C; ^{1}H NMR: $\delta = 10.56$ (s, 1H, NH), 9.80 (s, 1H, NH), 8.08 (s, 1H, arom CH), 7.65–7.73 (m, 2H, arom CH), 5.36 (s, 1H, CH), 4.04 (q, $J = 7.6$ Hz, 2H, OCH_2), 2.34 (s, 3H, CH_3), 1.11 (t, $J = 7.5$ Hz, 3H, CH_3); IR (KBr): 3170, 1715, 1661, 1593, 1540 cm^{-1}; Anal. calcd. for $C_{14}H_{15}N_3O_4S$: C, 52.33; H, 4.71; N, 13.08. Found: C, 52.34; H, 4.66; N, 13.15.

5-Ethoxycarbonyl-6-methyl-4-styryl-3,4-dihydropyrimidin-2(1*H*)-thione (4g): M.p. 223–225°C; ^{1}H NMR: $\delta = 10.13$ (s, 1H, NH), 9.46 (s,1H, NH), 7.31–7.56 (m, 5H, arom CH), 6.36 (d, $J = 15.7$ Hz, 1H, H–C=CH), 6.28 (dd, $J = 15.9$, 6.0 Hz, 1H, CH=C–H), 4.74 (d, $J = 5.70$ Hz, 1H, CH), 4.08 (m, 2H, OCH_2), 2.29 (s, 3H, CH_3), 1.21 (t, $J = 7.1$ Hz, 3H, CH_3); IR (KBr): 3242, 1706, 1653 cm^{-1}; Anal. calcd. for $C_{16}H_{18}N_2O_2S$: C, 63.55; H, 6.00; N, 9.26; Found: C, 63.56; H, 6.05; N, 9.22.

5-Ethoxycarbonyl-6-methyl-4-(2-phenylethane)-3,4-dihydropyrimidin-2(1*H*)-thione (4h): M.p. 167–169°C; ^{1}H NMR: $\delta = 10.22$ (s, 1H, NH), 9.23 (s, 1H, NH), 7.06–7.33 (m, 5H, arom CH), 4.20 (m, 1H, CH), 4.01 (m, 2H, OCH_2), 1.71 (t, 3H, CH_3), 2.20 (s, 3H, CH_3), 1.85 (m, 4H, CH_2CH_2); IR (KBr): 3245, 1700, 1635 cm^{-1}; Anal. calcd. for $C_{16}H_{20}N_2O_2S$: C, 63.13; H,6.62; N, 9.20. Found: C, 63.11; H, 6.60; N, 9.18.

4-Isopropyl-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione (4i): M.p. 191–192°C; ^{1}H NMR: $\delta = 10.05$ (s, 1H, NH), 9.21 (s, 1H, NH), 4.04 (m, 2H, OCH_2), 3.95 (t, $J = 3.5$ Hz, 1H, CH), 2.18 (s, 3H, CH_3), 1.66 (m, 1H, CH), 1.18 (t, $J = 7.1$ Hz, 3H, CH_3), 0.85 (d, $J = 6.9$ Hz, 3H, CH_3), 0.76 (d, $J = 6.8$ Hz, 3H, CH_3); IR (KBr): 3235, 3104, 1691, 1643 cm^{-1}; Anal. calcd. for $C_{11}H_{18}N_2O_2S$: C, 54.52; H, 7.49; N, 11.56. Found: C, 54.50; H, 7.46; N, 11.51.

4-Butyl-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione (4j): M.p. 185–187°C; ^{1}H NMR: $\delta = 10.10$ (s, 1H, NH), 9.25 (s, 1H, NH), 4.05 (m, 2H, OCH_2), 2.50 (s, 3H, CH_3), 1.15–1.39 (m, 9H, $(CH_2)_3CH_3$), 0.86 (t, $J = 6.5$ Hz, 3H, CH_3); IR (KBr): 3247, 1721, 1646 cm^{-1}; MS (70 eV, EI): m/z (%): 256 (M, 4), 199 (100); Anal. calcd. for $C_{12}H_{20}N_2O_2S$: C, 56.22; H, 7.86; N, 10.93. Found: C, 56.20; H, 7.81; N, 10.90.

5-Aceto-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-thione (4k): M.p. 220–221°C; ^{1}H NMR: $\delta = 10.16$ (s, 1H, NH), 9.66 (s, 1H, NH), 7.21–7.35 (m, 5H, arom CH), 5.23 (d, $J = 2.2$ Hz, 1H, CH), 2.23 (s, 3H, CH_3CO), 2.06 (s, 3H, CH_3); IR (KBr): 3254, 1693, 1672 cm^{-1}; Anal. calcd. for $C_{13}H_{14}N_2OS$: C, 63.39; H, 5.73; N, 11.37. Found: C, 63.35; H, 5.71; N, 11.33.

5-Methoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione (4l): M.p. 201–202°C; ^{1}H NMR: $\delta = 10.15$ (s, 1H, NH), 9.27 (d, $J = 3.1$ Hz, 1H, NH), 7.22–7.35 (m, 5H, arom CH), 5.16 (d, $J = 2.6$ Hz, 1H, CH), 3.52

(s, 3H, OCH_3), 2.25 (s, 3H, CH_3); IR (KBr): 3332, 1696, 1653 cm^{-1}; Anal. calcd. for $C_{13}H_{14}N_2O_2S$: C, 59.52; H, 5.38; N, 10.68. Found: C, 59.50; H, 5.36; N, 10.65.

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