Articles

One-Pot Syntheses of 3, 4-Dihydropyrimidine-2 (1*H*)-thiones Catalyzed by La(OTf)$_3$

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A general and practical procedure for the syntheses of 3,4-dihydropyrimidine-2(1*H*)-thiones by a one-pot condensation of aldehyde, β-ketoester or β-diketone and thiourea using La(OTf)$_3$ as the catalyst is described. Mild reaction conditions, excellent yields as well as the environmentally friendly character of La(OTf)$_3$ make it an important alternative to the classic acid-catalyzed Biginelli's reaction.

Keywords 3,4-dihydropyrimidine-2(1*H*)-thione, Biginelli's reaction, La(OTf)$_3$

Introduction

In recent years, dihydropyrimidinethione derivatives have attracted considerable interest due to their promising activities as anticarcinogenic agents,[1] cardiovascular agents[2] and calcium channel blockers.[3] In addition, some derivatives of dihydropyrimidinethione were patented as agents for the protection of wool against moths.[4] Thus, the synthesis of this heterocyclic nucleus is of current importance. In 1893, Biginelli reported a simple and straightforward procedure starting from β-dicarbonyl compounds, aldehyde and thiourea under strong acidic conditions with low yields (20%—50%).[5] Recently, several improved procedures for the preparation of DHPMs (Biginelli compounds) have been reported.[6] However, all these methods gave low yields and the catalyst could not be recovered. Lanthanide triflates are unique Lewis acids that are currently of great research interest. In our previous work, it was found that Ln(OTf)$_3$ is an efficient catalyst for two or three components condensation reactions.[7] As an extension of our exploratory research for the use of Yb(OTf)$_3$ to catalyze the one-pot synthesis of dihydropyrimidinones.[7(d)] Here, we report a one-pot synthesis of dihydropyrimidine-2(1*H*)-thiones catalyzed by 3 mol% La(OTf)$_3$ under solvent-free conditions, which is a simple, cheap, high-yielding, timesaving and environmentally friendly process.

Results and discussion

In a typical general experimental procedure, a mixture of aldehyde, β-dicarbonyl and thiourea was heated in a Schlenk tube at 100 ℃ under stirring in the presence of a catalytic amount of La(OTf)$_3$(3 mol%) for a certain period of time as required to complete the reaction. Then water was added into the reaction mixture, the solid product was filtered and recrystallized from ethanol.

Several structurally varied β-dicarbonyl compounds, aldehydes and thiourea are coupled together by this procedure to produce the corresponding dihydropyrimidine-2(1*H*)-thiones. The results are listed in Table 1. Both β-keto ester and β-diketone can react with aldehyde and thiourea readily. A variety of substituted aromatic aldehydes have been subjected to this condensation efficiently. All the lanthanide trifluoromethanesulfonates examined showed good catalytic activities. However, La(OTf)$_3$ was particularly effective for this reaction. 3 mol% of La(OTf)$_3$ was sufficient to provide the products in excellent

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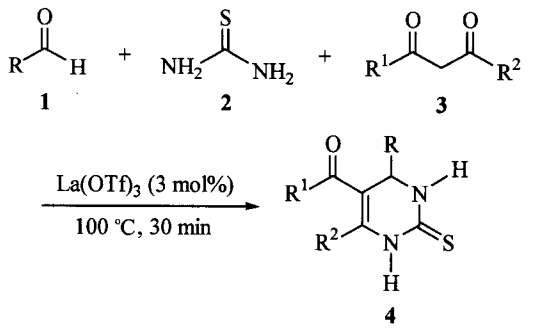
yields. More amount of $La(OTf)_3$ did not improve the results to a great extent. A catalyst loading of 2 mol% led to lower yields. This method is fairly general and the products are conveniently isolated by recrystallization. In addition, $La(OTf)_3$ can be easily recovered and reused.

Table 1 $La(OTf)_3$-catalyzed syntheses of 3,4-dihydropyrimidine-2(1*H*)-thiones[a]

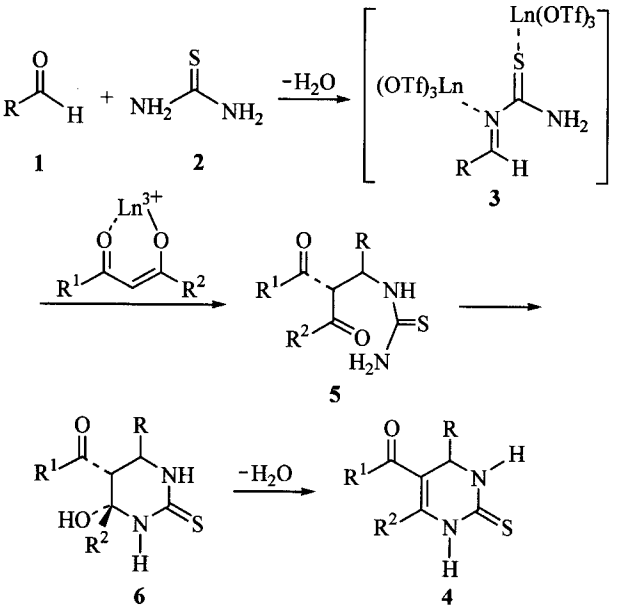


Entry	1	3		Product	Yield (%)[b]
	R	R^1	R^2		
1	C_6H_5	CH_3	C_2H_5O	**4a**	98
2	C_6H_5	CH_3	C_2H_5O	**4a**	97, 98, 98[c]
3	C_6H_5	CH_3	C_2H_5O	**4a**	80[d]
4	3-$CH_3C_6H_4$	CH_3	C_2H_5O	**4b**	96
5	4-$CH_3OC_6H_4$	CH_3	C_2H_5O	**4c**	93
6	3-$CH_3OC_6H_4$	CH_3	C_2H_5O	**4d**	93
7	3,4-$(CH_3O)_2C_6H_3$	CH_3	C_2H_5O	**4e**	94
8	4-ClC_6H_4	CH_3	C_2H_5O	**4f**	93
9	3-$NO_2C_6H_4$	CH_3	C_2H_5O	**4g**	89
10	C_6H_5	CH_3	CH_3	**4h**	96
11	4-$CH_3OC_6H_4$	CH_3	CH_3	**4k**	98
12	4-ClC_6H_4	CH_3	CH_3	**4m**	95
13	C_6H_5	CH_3	C_6H_5	**4n**	96

[a] $La(OTf)_3$ (3 mol%, based on aldehyde), 100 ℃ for 30 min; [b] isolated yields; [c] $La(OTf)_3$ was reused for 3 times; [d] $La(OTf)_3$(2 mol%), 100 ℃, 60 min.

The reaction mechanism was proposed as described in Scheme 1. Aldehyde reacts with thiourea to form an acyl imine intermediate which is activated by lanthanide coordination (the key and rate-limiting step). Subsequent addition of the β-carbonyl compound followed by cyclization and dehydration affords the dihydropyrimidinone.

Scheme 1



Experimental

General

Melting points were determined on a Kofler hot stage and were uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ with a VXL-300 or FX-90Q instrument. Infrared spectra were recorded on a Perkin-Elmer 983 FT-IR spectrometer. Mass spectral measurements were performed on a Finnigan 4021 or Finnigan MAT 8430 gas chromatograph/mass spectrometer at 70 eV and mass data were tabulated as *m/z* values. Elemental analyses were carried out on an MOD-1106 elemental analyzer.

General procedure for the syntheses of 3,4-dihydropyrimidine-2(1H)-thiones

A mixture of benzaldehyde (212 mg, 2.0 mmol), ethyl acetoacetate (260 mg, 2.0 mmol), thiourea (198 mg, 2.6 mmol) and $La(OTf)_3$ (35 mg, 0.06 mmol) was heated in a Schlenk tube at 100 ℃ under being stirred for 30 min. Water was added, the solid separated was filtered, washed with ice-cold water, and then recrystallized from hot ethanol to afford pure product **4a** (541 mg, 98%).

This procedure was followed for the preparation of all

the dihydropyrimidinethiones listed in Table 1. The m.p., spectral and analytical data of the new compound, have been presented below.

The catalyst remaining in the aqueous phase can be recovered by removing the water through evaporation and then being dried under vacuum at 100 ℃ for 3 h.

5-Ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidine-2(1H)-thione (**4a**) m.p. 205—206 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.18 (t, J = 7.1 Hz, 3H, CH_3), 2.41 (s, 3H, CH_3), 4.15 (q, J = 7.1 Hz, 2H, CH_2), 5.41 (s, 1H, CH), 7.50—7.55 (m, 5H, ArH), 7.75—7.78 (br, 1H, NH), 8.53—8.59 (br, 1H, NH); IR ν: 3175, 3107, 2980, 1671, 1575, 1466, 1371, 1328, 1284, 1197, 1177, 1119, 1028, 1002 cm^{-1}; MS *m/z* (%): 276(M^+, 100); Anal. calcd for $C_{14}H_{16}O_2N_2S$: C 60.86, H 5.80, N 10.14; found C 60.37, H 6.48, N 9.76.

5-Ethoxycarbonyl-4-(3-methylphenyl)-6-methyl-3,4-dihydropyrimidine-2(1H)-thione (**4b**) m.p. 172—173 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.06 (t, J = 7.0 Hz, 3H, CH_3), 2.22 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 3.97 (q, J = 7.0 Hz, 2H, CH_2), 5.11 (s, 1H, CH), 6.98—7.02 (m, 5H, ArH), 7.80—7.84 (br, 1H, NH), 8.48—8.54 (br, 1H, NH); IR ν: 3167, 1669 cm^{-1}; MS *m/z* (%): 290(M^+, 100); Anal. calcd for $C_{15}H_{18}O_2N_2S$: C 62.07, H 6.21, N 9.66; found C 61.89, H 6.14, N 9.51.

5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidine-2(1H)-thione (**4c**) m.p. 133—134 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.17 (t, J = 7.1 Hz, 3H, CH_3), 2.42 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 4.09 (q, J = 7.1 Hz, 2H, CH_2), 5.35 (s, 1H, CH), 6.89 (d, J = 8.6 Hz, 2H, ArH), 7.26 (d, J = 8.6 Hz, 2H, ArH), 7.96 (s, 1H, NH), 8.18 (s, 1H, NH); IR ν: 3171, 1668 cm^{-1}; MS *m/z* (%): 306(M^+, 13); Anal. calcd for $C_{15}H_{18}O_3N_2S$: C 58.82, H 5.88, N 9.15; found C 58.94, H 6.13, N 9.05.

5-Ethoxycarbonyl-4-(3-methoxyphenyl)-6-methyl-3,4-dihydropyrimidine-2(1H)-thione (**4d**) m.p. 151—152 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.12 (t, J = 7.1 Hz, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 4.04 (q, J = 7.1 Hz, 2H, CH_2), 5.85 (s, 1H, CH), 6.83—6.86 (m, 3H, ArH), 7.22 (t, J = 9 Hz, 1H, ArH), 9.70 (s, 1H, NH), 10.38 (s, 1H, NH); IR ν: 3122, 1712 cm^{-1}; MS *m/z* (%): 306(M^+, 13); Anal. calcd for $C_{15}H_{18}O_3N_2S$: C 58.82, H 5.88, N 9.15; found C 59.03, H 6.09, N 9.18.

5-Ethoxycarbonyl-4-(3,4-dimethoxyphenyl)-6-methyl-3,4-dihydropyrimidine-2(1H)-thione (**4e**) m.p. 152—153 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.12 (t, J = 7.2 Hz, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.79 (s, 6H, 2 × OCH_3), 3.98 (q, J = 7.2 Hz, 2H, CH_2), 5.29 (s, 1H, CH), 6.75—6.78 (m, 3H, ArH); IR ν: 3175, 1678 cm^{-1}; MS *m/z* (%): 336(M^+, 100); Anal. calcd for $C_{16}H_{20}O_4N_2S$: C 57.14, H 5.95, N 8.33; found C 57.23, H 6.08, N 8.19.

5-Ethoxycarbonyl-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidine-2(1H)-thione (**4f**) m.p. 162—163 ℃; ^{1}H NMR (Acetone-d_6, 300 MHz) δ: 1.21 (t, J = 7.1 Hz, 3H, CH_3), 2.44 (s, 3H, CH_3), 4.12 (q, J = 7.1 Hz, 2H, CH_2), 5.65 (s, 1H, CH), 7.37—7.41 (m, 4H, ArH), 9.51 (s, 1H, NH), 10.06 (s, 1H, NH); IR ν: 3176, 1673 cm^{-1}; Anal. calcd for $C_{14}H_{15}O_2N_2SCl$: C 54.11, H 4.83, N 9.02; found C 53.91, H 4.78, N 9.12.

5-Ethoxycarbonyl-4-(3-nitrophenyl)-6-methyl-3,4-dihydropyrimidine-2(1H)-thione (**4g**) m.p. 212—213 ℃; ^{1}H NMR (Acetone-d_6, 300 MHz) δ: 1.17(t, J = 7.0 Hz, 3H, CH_3), 2.40 (s, 3H, CH_3), 4.15 (q, J = 7.1 Hz, 2H, CH_2), 5.52 (s, 1H, CH), 7.63—8.17 (m, 4H, ArH), 8.80 (s, 1H, NH), 9.40 (s, 1H, NH); IR ν: 3183, 1716 cm^{-1}; MS *m/z* (%): 321(M^+, 78); Anal. calcd for $C_{14}H_{15}O_4N_3S$: C 52.34, H 4.67, N 13.08; found C 52.09, H 4.58, N 12.99.

5-Acetyl-4-phenyl-6-methyl-3,4-dihydropyrimidine-2(1H)-thione (**4h**) m.p. 220—221 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.90 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 5.07 (d, J = 4 Hz, 1H, CH), 7.04—7.07 (m, 5H, ArH), 9.53(s, 1H, NH), 10.06 (s, 1H, NH); IR ν: 3298, 3203, 2996, 1610, 1578, 1463, 1198, 1190, 1158, 1115, 1022, 944 cm^{-1}; MS *m/z* (%): 246(M^+, 100); Anal. calcd for $C_{13}H_{14}ON_2S$: C 63.41, H 5.69, N 11.37; found C 63.04, H 5.68, N 11.56.

5-Acetyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidine-2(1H)-thione (**4k**) m.p. 178—179 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.17(s, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 5.47 (s, 1H, CH), 6.91(d, J = 8.6 Hz, 2H, ArH), 7.28(d, J = 8.6 Hz, 2H, ArH), 9.65 (s, 1H, NH), 10.35 (s, 1H, NH); IR ν: 3234, 1620 cm^{-1}; MS

m/z (%): 276(M^+, 100), 275 (52); Anal. calcd for $C_{14}H_{16}O_2N_2S$: C 60.86, H 5.80, N 10.14; found C 60.81, H 6.16, N 10.03.

5-Acetyl-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidine-2(1H)-thione (**4m**) m.p. 224—225 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.25(s, 3H, CH_3), 2.47 (s, 3H, CH_3), 5.78 (d, J = 2.1 Hz, 1H, CH), 7.39—7.41 (m, 4H, ArH); IR ν: 3178, 1622 cm^{-1}; MS *m/z* (%): 280 (M^+, 100), 282 (38), 279 (47), 281 (32), 283 (6), 284 (2); Anal. calcd for $C_{13}H_{13}ON_2SCl$: C 55.61, H 4.63, N 9.98; found C 55.49, H 4.47, N 9.98.

5-Benzoyl-4-phenyl-6-methyl-3,4-dihydropyrimidine-2(1H)-thione (**4n**) m.p. 227—228 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.75(s, 3H, CH_3), 5.31 (d, J = 3 Hz, 1H, CH), 7.44—7.49 (m, 4H, ArH), 9.69 (s, 1H, NH), 10.35 (s, 1H, NH); IR ν: 3427, 1668, 1557, 1125 cm^{-1}; MS *m/z* (%): 308 (M^+, 100); Anal. calcd for $C_{18}H_{16}ON_2S$: C 70.10, H 5.23, N 9.08; found C 69.95, H 5.38, N 9.12.

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