An Efficient One-Pot Synthesis of Dihydropyrimidinones by a Samarium Diiodide Catalyzed Biginelli Reaction Under Solvent-Free Conditions

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The Biginelli reaction, a one-pot condensation of aldehydes, urea or thiourea, and β-dicarbonyl compounds, is efficiently catalyzed by samarium diiodide. The biologically active dihydropyrimidinones are easily synthesized in moderate to excellent yields under solvent-free conditions.

Introduction

The Biginelli reaction (Scheme 1), the direct synthesis of dihydropyrimidinones by the one-pot condensation of aldehydes, urea or thiourea, and β-dicarbonyl compounds, was first reported more than a century ago[1] and has not received much attention since. However, in the past decade the Biginelli reaction has attracted widespread attention because many dihydropyrimidinones and their derivatives have been found to possess various biological activities and can be widely used as calcium channel blockers, antihypertensive agents, and α_1-1-a-antagonists.[2,3] As a result, a variety of methods for promoting the Biginelli reaction, including catalytic reactions, solid-phase reactions,[4,5] and microwave irradiation,[6,7] have been developed. Among them, the Lewis acid catalyzed Biginelli reaction has achieved considerable success. $BF_3{\cdot}OEt_2$ in combination with CuCl,[8] $FeCl_3{\cdot}6H_2O$,[9] $LaCl_3{\cdot}7H_2O$,[10] $CeCl_3{\cdot}7H_2O$,[11] lanthanide triflates,[12,13] Yb^{III} resin,[14] or $InCl_3$[15] has been reported to be effective for this one-pot reaction. However, there are still some drawbacks in these catalytic systems, including the high cost of the catalyst, high catalyst loading, or the need for a solvent.

Samarium diiodide (SmI_2), which is cheap and easily prepared, is known to be an efficient Lewis acid-type precatalyst for a variety of carbon–carbon[16] and carbon–nitrogen[17–19] bond-forming reactions. As part of our continued interest in the application of samarium diiodide as a precatalyst in diverse reactions,[20–23] we examined its catalytic activity in the Biginelli reaction and found that it promotes the one-pot condensation of aldehydes, urea or thiourea, and β-dicarbonyl compounds. Herein we wish to report our results.

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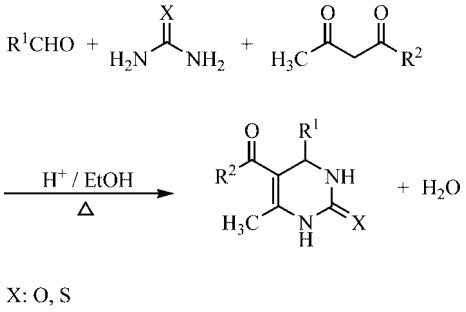

Scheme 1.

Results and Discussion

The reaction of benzaldehyde, urea, and ethyl acetoacetate was first tested using 20 mol-% samarium diiodide as the precatalyst at 100 °C for 1 h. The reaction went smoothly and the corresponding dihydropyrimidinone was obtained in 88% yield (Table 1, entry 1). The yield was still as high as 80% even when the amount of SmI_2 was reduced from 20 mol-% to 10 mol-%. The same process was successfully extended to a wide range of structurally varied aldehydes, urea or thiourea, and β-dicarbonyl compounds (Scheme 2); the corresponding dihydropyrimidinones were obtained in moderate to excellent yields. The results are listed in Table 1. As can be seen from this table, the reactions with both aromatic and heteroaromatic aldehydes, including alkyl-substituted aromatic aldehydes, yield the corresponding products in high yields (entries 1–3). However, the yield drops significantly when the aromatic aldehyde bears functional groups such as OH and OCH_3 on the benzene ring (entry 4). It is probable that the aldehyde carbonyl group becomes less active in the presence of electron-donating substituents. A similar influence can also be observed in the reaction involving cinnamaldehyde (entry 5).

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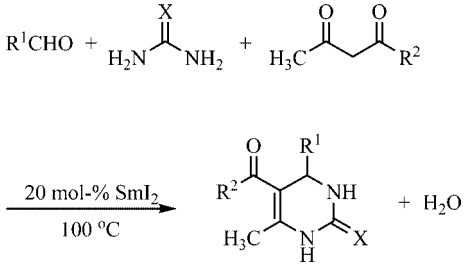
Table 1. Samarium diiodide catalyzed Biginelli reaction.

Entry[a]	R^1	R^2	X	Product	Isol. yield [%]
1	Ph	OEt	O	**4a**	88 (80[b])
2	4-CH_3Ph	OEt	O	**4b**	81
3	2-furyl	OEt	O	**4c**	84
4	4-(OH)-3-(OCH_3)-Ph	OEt	O	**4d**	39
5	PhCH=CH	OEt	O	**4e**	32
6	*n*Pr	OEt	O	**4f**	85
7	*i*Pr	OEt	O	**4g**	54
8	Ph	Me	O	**4h**	85[c]
9	2-furyl	Me	O	**4i**	72[c]
10	*n*Pr	Me	O	**4j**	75[c]
11	Ph	OEt	S	**4k**	95
12	4-CH_3Ph	OEt	S	**4l**	91
13	2-furyl	OEt	S	**4m**	83
14	*n*Pr	OEt	S	**4n**	88
15	*i*Pr	OEt	S	**4o**	87
16	Ph	Me	S	**4p**	67

[a] Typical reaction conditions: 20 mol-% SmI_2 relative to aldehyde, aldehyde/urea or thiourea/β-dicarbonyl compound = 1:1.5:1, 100 °C, 1 h, no solvent. [b] 10 mol-% SmI_2; yield determined by HPLC. [c] The reaction time was 9 h.



Scheme 2.

The reaction with aliphatic aldehydes is greatly influenced by steric effects. For example, the reaction of *n*-butyl aldehyde with urea and ethyl acetoacetate gave the product in 85% yield, while only 54% yield was obtained for isobutyl aldehyde (entries 6 and 7). Both ethyl acetoacetate and 2,4-pentanedione can be used as the β-dicarbonyl compound, although the latter is less active. Therefore, in order to get the desired yield of the corresponding dihydropyrimidinone using 2,4-pentanedione as substrate, the reaction time was prolonged from one hour to nine hours (entries 8–10). An X-ray diffraction analysis was performed to confirm the molecular structure of product **4j**,[24] the structure of which is shown in Figure 1. All the reactions with thiourea instead of urea proceeded very well and gave good yields (entries 11–16).

We noticed that the reaction with 1,1,1-trifluoroacetylacetone gave the intermediate **5h** as the only product in 71% yield (Scheme 3). To confirm its molecular structure (Figure 2), an X-ray diffraction analysis[24] was performed. A similar result has also been found in previous work with $Yb(OTf)_3$[12] as the catalyst.

When SmI_2 was mixed with the substrates, the color of the reaction system immediately turned from dark blue to yellow, which is indicative of the formation of a Sm^{III} active species. In order to determine the nature of this species, two

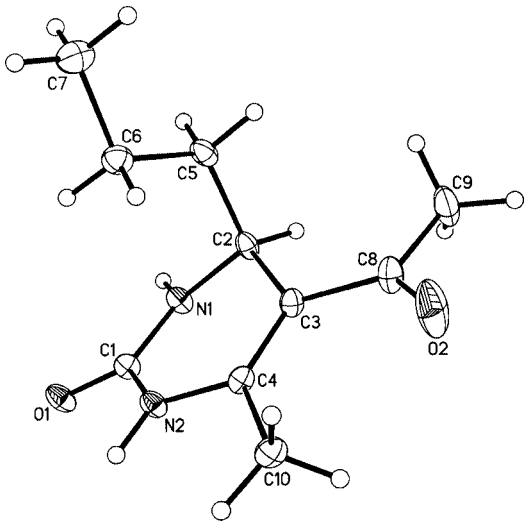
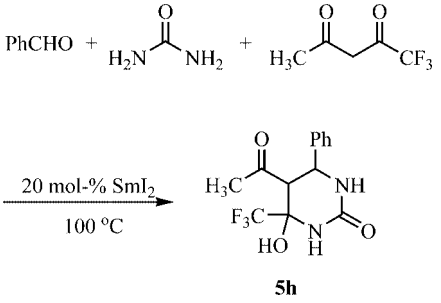


Figure 1. X-ray crystal structure of **4j**.



Scheme 3.

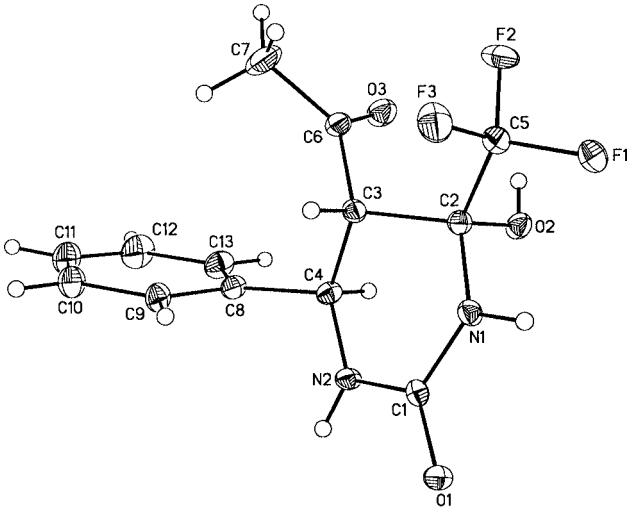
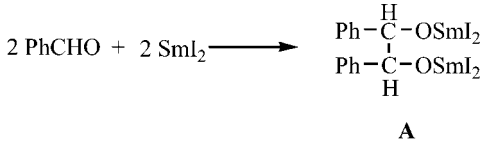


Figure 2. X-ray crystal structure of **5h**.

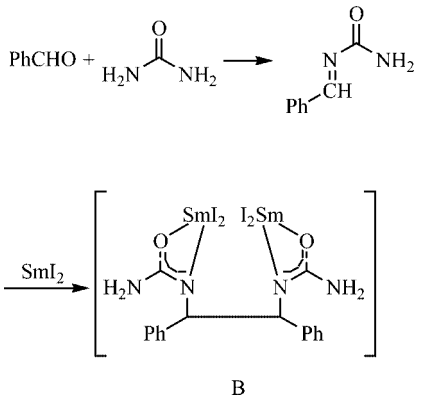
additional experiments were designed: (i) SmI_2 and benzaldehyde were mixed in a 1:1 molar ratio and this mixture was used as the catalyst (20 mol-%) in the reaction of benzaldehyde, urea and ethyl acetoacetate; (ii) a mixture of benzaldehyde and urea in a 1:1 ratio was stirred for 10 min followed by the addition of an equimolar amount of SmI_2 and this mixture was used as the catalyst (20 mol-%) in the same reaction mentioned in the first experiment. After work up,

the first reaction gave product **4a** in 59% yield, while the second one gave **4a** in 86% yield. The yield for the second reaction is almost equal to that (88%) obtained from the normal procedure (Table 1, entry 1), while for the first one it is much lower. These results indicate that the active species here is probably not the pinacol-Sm^{III} complex A[25,26] (Scheme 4) formed by the reaction of SmI_2 with benzaldehyde, but the intermediate B (Scheme 5) formed by the reaction of SmI_2 with the acyl imine generated from the condensation of aldehyde and urea. The suggested one-electron redox reaction of SmI_2 with acyl imine is similar to the ytterbium-mediated dehydrogenative coupling of aldimines described by Fujiwara et al.[27] Further studies on the mechanism are now in progress.



A

Scheme 4.



B

Scheme 5.

It is worth mentioning that all the reactions were carried out under solvent-free conditions, which not only avoids the consumption of solvent and simplifies the operation, but is also favorable for environmental conservation.

Conclusions

In conclusion, samarium diiodide has been found to be an efficient catalyst for the Biginelli reaction, which gives dihydropyrimidinones in moderate to excellent yields under solvent-free conditions. The simplicity of the catalytic procedure and its environmentally friendly nature make this catalytic reaction a potential, environmentally acceptable method for the synthesis of dihydropyrimidinones.

Experimental Section

General Remarks: All the manipulations were conducted under dry argon in flame-dried glassware. SmI_2 was synthesized by stirring a mixture of Sm metal and I_2 in a THF solution at room temperature for several hours.[28] Liquid aldehydes, ethyl acetate and 2,4-pentanedione were distilled prior to use. Other reagents were used as purchased without further purification. ^{1}H NMR spectra were obtained on Varian INOVA-400 spectrometer using TMS as internal reference. Elemental analyses were determined on a Carlo Erba EA1110-CHNS-O analyzer. Mass spectra were recorded on a Micromass GCT instrument. Melting points are uncorrected.

Typical Procedure: A mixture of aldehyde (2 mmol), urea or thiourea (3 mmol), β-dicarbonyl compound (2 mmol), and samarium diiodide (0.4 mmol, 20 mol-%) was heated at 100 °C whilst stirring for the given time. Water was then added and the mixture extracted with ethyl acetate. The organic layer was dried with anhydrous Na_2SO_4 and concentrated in vacuo. The residue was recrystallized from ethyl acetate and hexane to afford pure product. All new compounds were fully characterized by ^{1}H NMR spectroscopy, mass spectrometry, and elemental analysis.

Dihydropyrimidine 4b: M.p. 221–222 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 2.32–2.34 [m, 6 H, $ArCH_3$ and C(6)-CH_3], 4.08 (q, J = 7.2 Hz, 2 H, OCH_2), 5.38 [s, 1 H, C(4)-H], 5.50 (br. s, 1 H, NH), 7.11–7.22 (m, 4 H, ArH), 7.55 (br. s, 1 H, NH) ppm. MS (EI): m/z = 274 [M^+]. $C_{15}H_{18}N_2O_3$ (274.35): calcd. C 65.67, H 6.61, N 10.21; found C 65.56, H 6.74, N 10.02.

Dihydropyrimidine 4l: M.p. 199–200 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 2.33–2.35 [m, 6 H, C(6)-CH_3 and $ArCH_3$], 4.10 (m, 2 H, OCH_2), 5.36 [d, J = 2.4 Hz, 1 H, C(4)-H], 7.02 (br. s, 1 H, NH), 7.12–7.26 (m, 4 H, ArH), 7.58 (br. s, 1 H, NH) ppm. MS (EI): m/z = 290 [M^+]. $C_{15}H_{18}N_2O_2S$ (290.42): calcd. C 62.04, H 6.25, N 9.65; found C 62.44, H 6.53, N 9.70.

Dihydropyrimidine 4m: M.p. 230–231 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 2.38 [s, 3 H, C(6)-CH_3], 4.16 (m, 2 H, OCH_2), 5.50 (s, 1 H, furyl-H), 6.17 [d, J = 2.4 Hz, 1 H, C(4)-H], 6.30 (s, 1 H, furyl-H), 6.96 (br. s, 1 H, NH), 7.35 (s, 1 H, furyl-H), 7.52 (br. s, 1 H, NH) ppm. MS (EI): m/z = 266 [M^+]. $C_{12}H_{14}N_2O_3S$ (266.35): calcd. C 54.11, H 5.30, N 10.52; found C 54.22, H 5.39, N 10.31.

Dihydropyrimidine 4n: M.p. 188.5–190 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 1.34 (m, 4 H, CH_2CH_2), 1.62 [t, J = 10.5 Hz, 3 H, $(CH_2)_2CH_3$], 2.31 [s, 3 H, C(6)-CH_3], 4.20 (m, 2 H, OCH_2), 4.37 [t, J = 3.2 Hz, 1 H, C(4)-H], 7.05 (br. s, 1 H, NH), 7.56 (br. s, 1 H, NH) ppm. MS (EI): m/z = 242 [M^+]. $C_{11}H_{18}N_2O_2S$ (242.38): calcd. C 54.51, H 7.49, N 11.56; found C 54.13, H 7.37, N 11.47.

Dihydropyrimidine 4o: M.p. 172–173 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (m, 6 H, $CHMe_2$), 1.29 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 1.88 (m, 1 H, $CHMe_2$), 2.31 [s, 3 H, C(6)-CH_3], 4.22 [m, 3 H, C(4)-H and OCH_2], 7.01 (br. s, 1 H, NH), 7.57 (br. s, 1 H, NH) ppm. MS (EI): m/z = 242 [M^+]. $C_{11}H_{18}N_2O_2S$: calcd. C 54.51, H 7.49, N 11.56; found C 54.81, H 7.77, N 11.59.

5h: M.p. 173–174 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67 (s, 3 H, CH_3), 3.38 (d, J = 11.2 Hz, 1 H, CH), 4.79 (d, J = 10.8 Hz, 1 H, CH), 5.46 (br. s, 1 H, NH), 5.72 (br. s, 1 H, OH), 6.06 (br. s, 1 H, NH), 7.34–7.42 (m, 5 H, ArH) ppm. MS (EI): m/z = 302 [M^+]. $C_{13}H_{13}F_3N_2O_3$ (302.28): calcd. C 51.66, H 4.34, N 9.27; found C 51.35, H 4.36, N 9.06.

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