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Indium(III) bromide-catalyzed preparation of dihydropyrimidinones: improved protocol conditions for the Biginelli reaction

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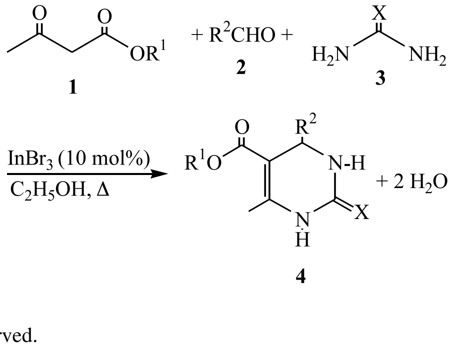
Abstract—Indium(III) bromide efficiently catalyzes the three-component coupling of β-keto esters, aldehydes and urea (or thiourea) to afford the corresponding dihydropyrimidinones. This new protocol for the Biginelli reaction includes the following important features: produces excellent yields, allows the recycling of catalyst with no loss in its activity, and leads to zero-discharge during the process. The reaction of ethyl acetoacetate, salicylaldehyde and thiuourea produced 13-ethoxycarbonyl-9-methyl-11-thioxo-8-oxa-10,12-diazatricyclo [7.3.1.0^{2,7}]-trideca-2,4-6-triene, which had its crystal structure determined by X-ray crystallography. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

Biginelli-type dihydropyrimidinones (DHPMs), **4** (Eq. (1)) have interesting pharmacological properties, such as efficacy as calcium channel modulators and α_{1a} adrenoaceptor-selective antagonists;[1] use as an anticancer drug capable of inhibiting kinesin motor protein;[2] and anti-HIV activity in some marine natural products, containing the DHPM skeleton, such as the alkaloid batzelladine B.[3] The original Biginelli protocol for the preparation of the DHPMs consisted of heating a mixture of the three components (β-keto-ester **1**, aldehyde **2**, and urea **3**) in ethanol containing a catalytic amount of HCl.[4] This procedure leads in one step-one pot to the desired DHPM. The major drawback associated with this protocol is the low yields, particularly for substituted aromatic and aliphatic aldehydes. Recently, there was considerable activity aiming to improve the efficiency of the Biginelli DHPMs synthesis. Yields have been improved compared to the original procedure by refluxing a mixture of the three starting materials in THF containing polyphosphate ester (PPE).[5] Use of Lewis acid catalysts ($BF_3{\cdot}OEt_2$,[6] $FeCl_3$ and HCl,[7] $LaCl_3{\cdot}7H_2O$,[8] and ytterbium triflate[9]) also gave improved yields.

We wish to report here a new study on the Biginelli reaction catalyzed by indium(III) compounds. After we had initiate our experiments, Ranu and co-workers reported the preparation of DHPMs catalyzed by $InCl_3$.[10] As in the case of the trichloride catalyst, we have found that indium(III) bromide is also efficient for preparing the DHPMs. However, the present protocol, involving the tribromide, includes new features related to Ranu's work, particularly from the preparative point of view. Remarkable advantages are: anhydrous conditions are no longer necessary during the process; in fact, the reactions were carried out in 95% ethanol; the catalyst can be re-used for several times without any decrease in reaction yields; and the procedure can be repeated with zero-discharge to the environment. Lastly, we have observed that in our hands the product from reactions involving salicylaldehyde, ethylacetoacetate and urea (or thiourea) is in fact the diazatricyclic compound 13-ethoxycarbonyl-9-methyl-11-oxo(or thioxo)-8-oxa-10,12-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene. The crystal structure of the thiourea derivative was solved by single crystal X-ray diffraction techniques.



(1)

Keywords: indium(III) bromide; green Lewis acid catalyst; Biginelli reaction.

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Table 1. $InBr_3$-catalyzed synthesis of **4a** under different reaction conditions

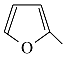
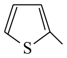
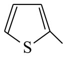
Entry	Solvent	Amount of $InBr_3$ (mol%)	Refluxing time (h)	Yield (%)[a]
1	THF	10	7	83
2	Toluene	10	0.5	56
3	Benzene	10	5.5	94
4	Dichloromethane	10	7	35
5	Water	10	0.5	Trace
6	Water/ethanol (1:1, v/v)	10	7	17
7	Ethanol	10	7	95, 98, 97, 96[b]
8	Ethanol	5	7	74[c]
9	Ethanol	2.5	7	66[d]
10	Ethanol	0	7	13

[a] Isolated yield.
[b] Catalyst was reused for four times.
[c] After filtering the product, the filtrate was heated under reflux for another 24 h, more product was obtained and the total yield came upto 97%.
[d] After filtering the product, the filtrate was heated under reflux for another 24 h, more product was obtained, the total yield came upto 98%.

2. Results and discussion

We started to study the three component Biginelli condensation catalyzed by $InBr_3$ (Eq. (1)) by examining the conditions for the reaction involving benzaldehyde, urea and ethylacetoatate to afford the DHPM **4a** (R^1=Et, R^2=Ph, X=O).

Table 2. Indium (III) bromide catalyzed synthesis of dihydropyrimidinones **4**

Product	R^1	R^2	X	Yield (%)[a]
4a	Et	Ph	O	98, (92, 96, 94)[b]
4b	Et	4-(OMe)–C_6H_4	O	97
4c	Et	2-(Me)–C_6H_4	O	94
4d	Et	4-(Me)–C_6H_4	O	98
4e	Et	3-(OH)–C_6H_4	O	90
4f	Et	4-(OH)–C_6H_4	O	93
4g	Et	2-(Cl)–C_6H_4	O	75
4h	Et	3-(Cl)–C_6H_4	O	70
4i	Et	4-(Cl)–C_6H_4	O	86
4j[c]	Et	3-(NO_2)–C_6H_4	O	95
4k[c]	Et	4-(NO_2)–C_6H_4	O	86
4l	Et		O	95
4m	Et		O	90
4n	Et	Ph-CH=CH	O	68
4o[d]	Et	Me	O	75
4p	Et	*n*-Bu	O	92
4q	Et	H	O	80
4r	Me	Ph	O	98
4s	Me	4-(OMe)–C_6H_4	O	94
4t	Me	4-(Me)–C_6H_4	O	97
4u	Me	4-(Cl)–C_6H_4	O	93
4v	Me	4-(NO_2)–C_6H_4	O	72
4w	Et	Ph	S	94
4x	Et	4-(OMe)–C_6H_4	S	98
4y	Et	4-(Me)–C_6H_4	S	94
4a	Et	4-(Cl)–C_6H_4	S	79
4a′	Et	4-(NO_2)–C_6H_4	S	70
4b′	Et		S	86
4c′	Et	H	S	70

[a] Isolated yield.
[b] Three consecutive condensations catalyzed by $InCl_3 \cdot 4H_2O$ (10 mol%).
[c] The refluxing time extended to 36 h in order to get satisfactory yield.
[d] From 40% acetaldehyde.

A summary of the optimization experiments is provided in Table 1. Entries 1–7 show the effect of various solvents on the reaction. THF (entry 1, 83%), benzene (entry 3, 94%) and 95% ethanol (entry 7, 98%) gave the highest yields. Ethanol was chosen as the solvent with consideration to the reaction yields and environmental impact. The optimum amount of catalyst (10 mol%) was determined from the experiments corresponding to entries 7–10. Entry 7 also describes the yields of four consecutive condensations leading to **4a**. In these experiments, the product **4a** was isolated by filtration, the filtered solution containing the 10 mol% of catalyst was reloaded with the initial reagents and this solution was re-submitted to a new period of reflux. No decrease in the yield was observed, demonstrating that $InBr_3$ can be reused as catalyst in a Biginelli condensation with zero-discharge to the environment.

Table 2 shows the generality of the present protocol, which is equally effective for urea and thiourea. In most cases, the reactions proceeded smoothly to produce the corresponding DHPMs in high yields. Aromatic aldehydes containing either electron-donating or electron-withdrawing substituents and aliphatic aldehydes all produced improved yields as compared to the classical Biginelli protocol. Surprisingly, even paraformaldehyde gave the corresponding DHPMs **4q** and **4c′**.

In the course of our work, we have observed that the products derived from the condensation reactions involving salicylaldehyde (Table 3) showed NMR spectra inconsistent with the expected DHPM structure. A single crystal X-ray structural analysis of the thiourea and ethylacetoacetate derivative, **5a** was conducted. Fig. 1 shows the molecular structure, proposed in earlier studies and based on NMR spectroscopy.[11,12]

Table 3. Indium(III) tribromide catalyzed synthesis of diazatricyclo compounds, **5** from alkylacetoacetate, salicylaldehyde and urea (or thiourea)

Product	R^1	X	Yield (%)[a]
5a	C_2H_5	S	70
5b	C_2H_5	O	75, 48[b]
5c	CH_3	O	72

[a] Isolated yield.
[b] Catalyzed by $InCl_3 \cdot 4H_2O$ (10 mol%).

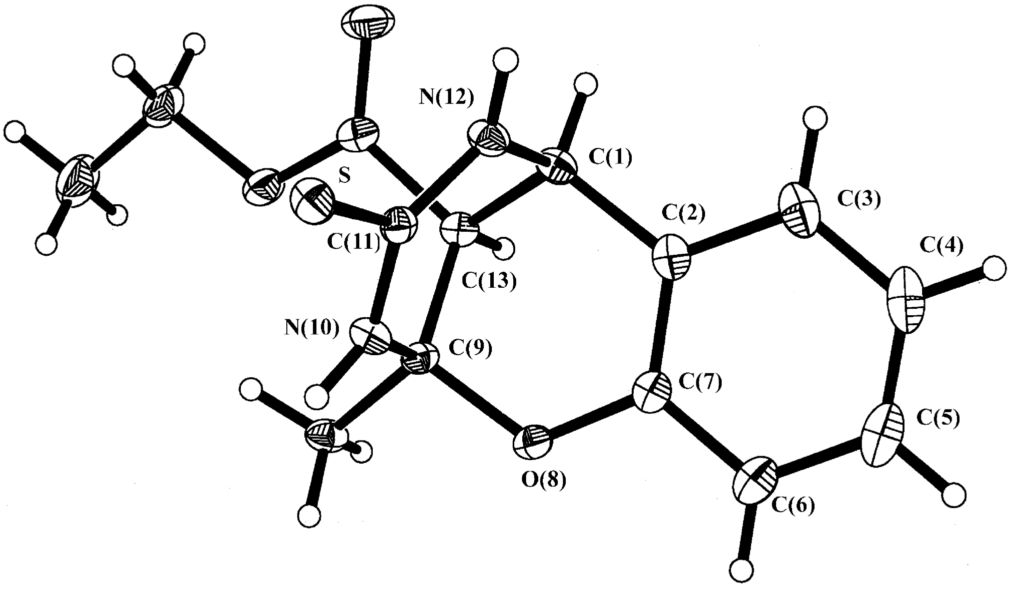
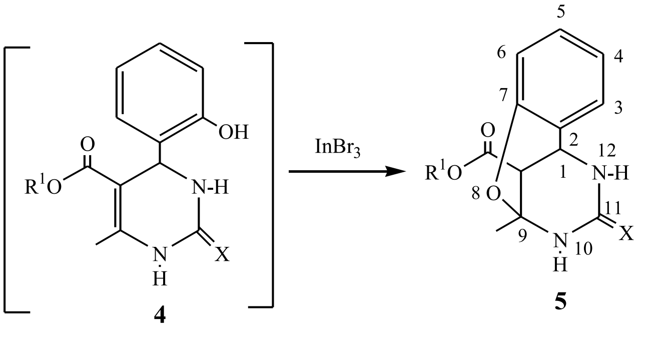


Figure 1. The molecular structure of $C_{14}H_{16}O_3N_2S$, **5a**, (ORTEP diagram), with non-hydrogen atoms shown as 30% probability ellipsoids.

The production of compounds **5a–c** can be explained by the isomerization reaction of the DHPM's, **4** which were initially formed (Scheme 1).

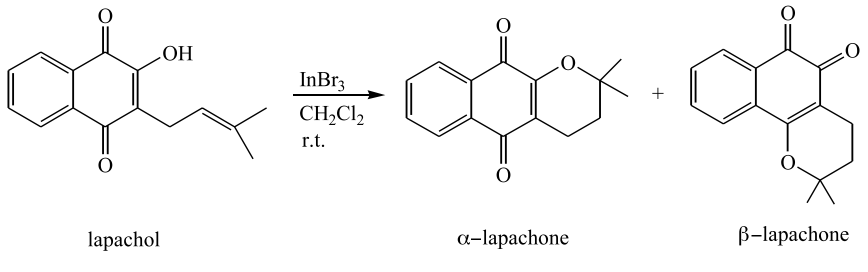
The preparation of the DHPM **4** derived from salicylaldehyde was first decribed in 1932.[13] Its structure was disproved in 1991, when exclusive formation of **5b** was obtained under HCl catalysis.[12] This finding suggests that this DHPM promptly isomerizes to its cyclic isomer in the presence of a Lewis acid. In support of this, we have demonstrated the ability of $InBr_3$ to catalyze the cyclization of a related system: lapachol was isomerized into α and β-lapachones (Scheme 2) in 87% of yield (α/β=1:5).



Scheme 1. The isomerization of DHPMs to diazatricyclic compounds.

The interest to develop new protocols to prepare organic compounds in aqueous media is growing during the last few years, since water is a non-toxic and environmentally benign solvent.[14] In this context, Lewis acid catalyzed processes is one of these challenges, particularly due to the fact that many Lewis acids promptly react with water, restricting their use. We had shown that $InBr_3$ acts as a catalyst in dithioacetalization of carbonyl compounds in aqueous media;[15] and in order to demonstrate the use of indium trihalides as 'green Lewis acid' catalysts for the Biginelli condensation, we have carried out: the preparation of **4o** from aqueous (40%) acetaldehyde; three consecutive condensations, catalyzed by $InCl_3 \cdot 4H_2O$, which produced **4a** in 92, 96 and 94% of yields; and the synthesis of **5b** in 48% using the hydrated catalyst. The experimental conditions for these experiments were those described in Tables 2 and 3, respectively. The sum of these results clearly indicates that InX_3 (X=Cl, Br) are equally efficient as catalysts in the Biginelli condensation reaction and that both can tolerate the presence of water in the media with no sign of deactivation.

In conclusion, the present procedure described useful improvements in the protocol conditions for the Biginelli condensations catalyzed by indium(III) halides. It introduced indium(III) bromide as a new catalyst, as efficient as the chloride analogue. Excellent reactional yields, recycling of the catalyst with no loss in its activity,



Scheme 2. The isomerization of lapachol–lapachone catalyzed by $InBr_3$.

zero-discharge to the environment, use of aqueous solvent and the elimination of anhydrous atmosphere during the reactions, are important features of this new protocol to prepare the Biginelli-type dihydropyrimidinones.

3. Experimental

Melting points were determined on a glass disk and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 solutions, unless otherwise indicated, on a BRUKER AC-P-200 spectrometer with TMS as internal standard. IR spectra were obtained on a FTS-135 spectrometer with KBr plates. Mass spectra were determined under EI (70 eV) on a VG-ZAB-HS spectrometer. Elemental analyses were carried out on a Perkin-Elmer 240 C analyzer. Indium(III) bromide was prepared by passing a flow of bromine gas through melted indium.[16] β-Keto esters, aldehydes, urea and thiourea were all commercial products and were used without further purification. All liquid reagents were distilled before use.

3.1. General procedure for the synthesis of DHPMs

Representative procedure for 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one, **4a**: a solution of ethyl acetoacetate (520 mg, 4 mmol), benzaldehyde (424 mg, 4 mmol), urea (312 mg, 5.2 mmol), $InBr_3$ (142 mg, 0.4 mmol) in 95% ethanol (10 mL) was heated under reflux for 7 h. On cooling, the product spontaneously crystallized from the solution. The pure solid **4a** (1.02 g, 3.92 mmol, 98%, mp 202–204°C, lit.[6] 202–204°C) was filtered, washed with ethanol (3×10 mL) and dried under vacuum. This procedure was followed for the preparation of all compounds **4** and **5** listed in Tables 2 and 3, respectively. Melting points, spectral and analytical data for these products are given below.

3.1.1. 5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one, 4a. Mp 202–204°C, lit.[6] 202–204°C; ^{1}H NMR: δ=9.20 (s, 1H, N*H*), 7.74 (s, 1H, N*H*), 7.25 (s, 5H, C_6H_5), 5.14 (s, 1H, C*H*), 3.97 (q, *J*=6.5 Hz, 2H, OCH_2CH_3), 2.24 (s, 3H, CH_3), 1.08 (t, *J*=6.5 Hz, 3H, OCH_2CH_3).

3.1.2. 5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one, 4b. Mp 202–204°C, lit.[6] 201–203°C; ^{1}H NMR: δ=9.14 (s, 1H, N*H*), 7.66 (s, 1H, N*H*), 7.15–6.84 (m, 4H, C_6H_4), 5.07 (s, 1H, C*H*), 3.96 (q, *J*=6.8 Hz, 2H, OCH_2CH_3), 3.70 (s, 3H, OCH_3), 2.23 (s, 3H, CH_3), 1.09 (t, *J*=6.8 Hz, 3H, OCH_2CH_3).

3.1.3. 5-Ethoxycarbonyl-6-methyl-4-(2-methylphenyl)-3,4-dihydropyrimidin-2(1*H*)-one, 4c. Mp 208–210°C; ^{1}H NMR: δ=9.15 (s, 1H, N*H*), 7.84 (s, 1H, N*H*), 7.15–7.11 (m, 4H, C_6H_4), 5.39 (s, 1H, C*H*), 3.87 (q, *J*=7.0 Hz, 2H, OCH_2CH_3), 2.40 (s, 3H, $C_6H_5{-}CH_3$), 2.28 (s, 3H, CH_3), 0.98 (t, *J*=7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR: δ=165.3, 151.6, 148.4, 143.3, 134.7, 130.1, 127.2, 126.6, 99.3, 59.1, 50.6, 18.7, 17.7, 13.9; IR (KBr): 3155, 1686, 1628 cm^{-1}; MS (70 eV, EI): *m/z* (%): 274 (M, 41), 183 (100); Anal. (%): calcd for $C_{15}H_{18}O_3N_2$: C, 65.66; H, 6.62; N, 10.22. Found: C, 65.50; H, 6.85; N, 10.30.

3.1.4. 5-Ethoxycarbonyl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1*H*)-one, 4d. Mp 215–216°C; ^{1}H NMR: δ=9.15 (s, 1H, N*H*), 7.80 (s, 1H, N*H*), 7.10 (s, 4H, C_6H_4), 5.09 (s, 1H, C*H*), 3.96 (q, *J*=7.1 Hz, 2H, OCH_2CH_3), 2.23 (s, 3H, $C_6H_5{-}CH_3$), 1.08 (t, *J*=7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR: δ=165.3, 152.2, 148.1, 141.9, 136.3, 128.8, 126.1, 99.5, 59.1, 53.7, 20.6, 17.7, 14.1; IR (KBr): 3165, 1688, 1633 cm^{-1}; MS (70 eV, EI): *m/z* (%): 274 (M, 28), 183 (100); Anal. (%): calcd for $C_{15}H_{18}O_3N_2$: C, 65.66; H, 6.62; N, 10.22. Found: C, 65.39; H, 6.69; N, 10.13.

3.1.5. 5-Ethoxycarbonyl-4-(3-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one, 4e. Mp 163–165°C, lit.[10] 164–166°C; ^{1}H NMR: δ=9.38 (s, 1H, O*H*), 9.15 (s, 1H, N*H*), 7.64 (s, 1H, N*H*), 7.09–6.64 (m, 4H, C_6H_4), 5.04 (s, 1H, C*H*), 3.98 (q, *J*=7.0 Hz, 2H, OCH_2CH_3), 2.22 (s, 3H, CH_3), 1.11 (t, *J*=7.0 Hz, 3H, OCH_2CH_3).

3.1.6. 5-Ethoxycarbonyl-4-(4-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one, 4f. Mp 230–232°C, lit.[6] 230–232°C; ^{1}H NMR: δ=9.34 (s, 1H, O*H*), 9.10 (s, 1H, N*H*), 7.64 (s, 1H, N*H*), 7.03–6.65 (m, 4H, C_6H_4), 5.02 (s, 1H, C*H*), 3.96 (q, *J*=7.0 Hz, 2H, OCH_2CH_3), 2.21 (s, 3H, CH_3), 1.08 (t, *J*=7.0 Hz, 3H, OCH_2CH_3).

3.1.7. 4-(2-Chlorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one, 4g. Mp 222–224°C; ^{1}H NMR: δ=9.25 (s, 1H, N*H*), 7.70 (s, 1H, N*H*), 7.37–7.29 (m, 4H, C_6H_4), 5.61 (s, 1H, C*H*), 3.87 (q, *J*=6.9 Hz, 2H, OCH_2CH_3), 2.28 (s, 3H, CH_3), 0.97 (t, *J*=6.9 Hz, 3H, OCH_2CH_3); ^{13}C NMR: δ=165.0, 151.4, 149.3, 141.7, 131.8, 129.4, 129.1, 128.8, 127.7, 98.0, 59.1, 51.6, 17.7, 13.9; IR (KBr): 3150, 1688, 1626 cm^{-1}; MS (70 eV, EI): *m/z* (%): 294 (M, 14), 183 (100); Anal. (%): calcd for $C_{14}H_{15}O_3N_2Cl$: C, 57.03; H, 5.13; N, 9.51. Found: C, 56.89; H, 5.44; N, 9.30.

3.1.8. 4-(3-Chlorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one, 4h. Mp 193–195°C; ^{1}H NMR: δ=9.24 (s, 1H, N*H*), 7.77 (s, 1H, N*H*), 7.36–7.17 (m, 4H, C_6H_4), 5.14 (s, 1H, C*H*), 3.98 (q, *J*=7.0 Hz, 2H, OCH_2CH_3), 2.24 (s, 3H, CH_3), 1.08 (t, *J*=7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR: δ=165.2, 151.9, 148.9, 147.2, 132.9, 130.4, 127.2, 126.2, 124.9, 98.7, 59.3, 53.6, 17.8, 14.0; IR (KBr): 3350, 3140, 1692, 1635 cm^{-1}; MS (70 eV, EI): *m/z* (%): 294 (M, 18), 183 (100); Anal. (%): calcd for $C_{14}H_{15}O_3N_2Cl$: C, 57.03; H, 5.13; N, 9.51. Found: C, 56.96; H, 5.34; N, 9.34.

3.1.9. 4-(4-Chlorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one, 4i. Mp 212–214°C, lit.[6] 213–215°C; ^{1}H NMR: δ=9.24 (s, 1H, N*H*), 7.78 (s, 1H, N*H*), 7.40–7.21 (m, 4H, C_6H_4), 5.12 (s, 1H, C*H*), 3.97 (q, *J*=6.9 Hz, 2H, OCH_2CH_3), 2.24 (s, 3H, CH_3), 1.08 (t, *J*=6.9 Hz, 3H, OCH_2CH_3).

3.1.10. 5-Ethoxycarbonyl-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one, 4j. Mp 229–231°C; ^{1}H NMR: δ=9.37 (s, 1H, N*H*), 7.90 (s, 1H, N*H*), 8.10–7.64 (m, 4H, C_6H_4), 5.29 (s, 1H, C*H*), 3.98 (q, *J*=6.9 Hz, 2H, OCH_2CH_3), 2.26 (s, 3H, CH_3), 1.08 (t, *J*=6.9 Hz, 3H, OCH_2CH_3); ^{13}C NMR: δ=165.1, 151.9, 149.4, 147.8, 147.0, 133.0, 130.2, 122.3, 121.1, 98.4, 59.4, 53.6, 17.9, 14.0; IR (KBr): 3270, 1691, 1676, 1615, 1513 cm^{-1}; MS (70 eV, EI): *m/z* (%): 305 (M, 12), 183 (100); Anal. (%): calcd for $C_{14}H_{15}O_5N_3$: C, 55.06; H, 4.96; N, 13.77. Found: C, 55.11; H, 4.83; N, 13.81.

3.1.11. 5-Ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one, 4k. Mp 207–209°C, lit.[6] 208–211°C; ^{1}H NMR: δ=9.35 (s, 1H, N*H*), 7.89 (s, 1H, N*H*), 8.23–7.47 (m, 4H, C_6H_4), 5.26 (s, 1H, C*H*), 3.97 (q, *J*=7.0 Hz, 2H, OCH_2CH_3), 2.25 (s, 3H, CH_3), 1.08 (t, *J*=7.0 Hz, 3H, OCH_2CH_3).

3.1.12. 5-Ethoxycarbonyl-4-(2-furfuryl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one, 4l. Mp 209–211°C; ^{1}H NMR: δ=9.24 (s, 1H, N*H*), 7.75 (s, 1H, N*H*), 7.54 (s, 1H, $CH_{ar.}$), 6.34 (s, 1H, $CH_{ar.}$), 6.08 (s, 1H, $CH_{ar.}$), 5.19 (s, 1H, C*H*), 4.01 (q, *J*=6.9 Hz, 2H, OCH_2CH_3), 2.22 (s, 3H, CH_3), 1.12 (t, *J*=6.9 Hz, 3H, OCH_2CH_3); ^{13}C NMR: δ=165.0, 155.9, 152.4, 149.2, 142.1, 110.3, 105.2, 96.8, 59.2, 47.7, 17.7, 14.1; IR (KBr): 3320, 3225, 3100, 1695, 1640 cm^{-1}; MS (70 eV, EI): *m/z* (%): 250 (M, 80), 221 (M$-C_2H_5$, 99), 177 (100); Anal. (%): calcd for $C_{12}H_{14}O_4N_2$: C, 57.57; H, 5.64; N, 11.20. Found: C, 57.63; H, 5.59; N, 11.28.

3.1.13. 5-Ethoxycarbonyl-6-methyl-4-(2-thienyl)-3,4-dihydropyrimidin-2(1*H*)-one, 4m. Mp 215–217°C; ^{1}H NMR: δ=9.31 (s, 1H, N*H*), 7.88 (s, 1H, N*H*), 7.34 (d, *J*=5.3 Hz, 1H, $CH_{ar.}$), 6.93–6.88 (m, 2H, $CH_{ar.}$), 5.39 (s, 1H, C*H*), 4.05 (q, *J*=7.1 Hz, 2H, OCH_2CH_3), 2.20 (s, 3H, CH_3), 1.15 (t, *J*=7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR: δ= 165.0, 152.2, 148.8, 148.6, 126.6, 124.6, 123.5, 99.8, 59.3, 49.4, 17.7, 14.1; IR (KBr): 3165, 1680, 1633 cm^{-1}; MS (70 eV, EI): *m/z* (%): 266 (M, 84), 237 (M$-C_2H_5$, 100), 193 (91); Anal. (%): calcd for $C_{12}H_{14}O_3N_2S$: C, 54.10; H, 5.30; N, 10.52. Found: C, 54.27; H, 5.19; N, 10.33.

3.1.14. 5-Ethoxycarbonyl-6-methyl-4-styryl-3,4-dihydropyrimidin-2(1*H*)-one, 4n. Mp 225–227°C (dec.), lit.[13] 225°C (dec.); ^{1}H NMR: δ=9.09 (s, 1H, N*H*), 7.40 (s, 1H, N*H*), 7.37–7.21 (m, 5H, C_6H_5), 6.32 (d, *J*=12.0 Hz, 1H, =C*H*), 6.21 (dd, *J*=12.0, 5.8 Hz, 1H, =C–*H*), 4.72 (d, *J*=5.5 Hz, 1H, C*H*), 4.08 (q, *J*=7.0 Hz, 2H, OCH_2CH_3), 2.19 (s, 3H, CH_3), 1.19 (t, *J*=7.0 Hz, 3H, OCH_2CH_3).

3.1.15. 5-Ethoxycarbonyl-4,6-dimethyl-3,4-dihydropyrimidin-2(1*H*)-one, 4o. Mp 194–195°C; ^{1}H NMR: δ=8.97 (s, 1H, N*H*), 7.19 (s, 1H, N*H*), 4.06 (q, *J*=6.9 Hz, 3H, overlapped signals OCH_2CH_3 and $CHCH_3$), 2.15 (s, 3H, CH_3), 1.18 (t, *J*=6.9 Hz, 3H, OCH_2CH_3), 1.09 (d, *J*=6.0 Hz, 3H, CH_3); ^{13}C NMR: δ=165.3, 152.7, 147.6, 100.6, 59.1, 46.4, 23.3, 17.6, 14.2; IR (KBr): 3252, 3118, 1707, 1657 cm^{-1}; MS (70 eV, EI): *m/z* (%): 198 (M, 10), 237 (M$-CH_3$, 100), 193 (91); Anal. (%): calcd for $C_9H_{14}O_3N_2$: C, 54.51; H, 7.12; N, 14.14. Found: C, 54.65; H, 7.07; N, 14.23.

3.1.16. 4-Butyl-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one, 4p. Mp 164–166°C, lit.[9] 157–158°C; ^{1}H NMR: δ=8.92 (s, 1H, N*H*), 7.30 (s, 1H, N*H*), 4.03 (m, 3H, C*H*, OCH_2CH_3), 2.14 (s, 3H, CH_3), 1.36–1.13 (m, 9H, $-(CH_2)_3$, OCH_2CH_3), 0.83 (t, 3H, CH_3).

3.1.17. 5-Ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one, 4q. Mp 242–244°C (dec.); ^{1}H NMR: δ=8.84 (s, 1H, N*H*), 6.96 (s, 1H, N*H*), 4.03 (q, *J*=6.9 Hz, 2H, OCH_2CH_3), 3.86 (s, 2H, CH_2), 2.13 (s, 3H, CH_3), 1.16 (t, *J*=6.9 Hz, 3H, OCH_2CH_3); ^{13}C NMR (d^6-DMSO+$CDCl_3$): δ=165.3, 152.8, 148.4, 94.5, 59.0, 17.4, 14.2; IR (KBr): 3200, 3180, 1724, 1696, 1648 cm^{-1}; MS (70 eV, EI): *m/z* (%): 184 (M, 48), 155 (M$-C_2H_5$, 100), 111 (84); Anal. (%): calcd for $C_8H_{12}O_3N_2$: C, 52.17; H, 6.57; N, 15.22. Found: C, 52.31; H, 6.62; N, 15.07.

3.1.18. 5-Methoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one, 4r. Mp 206–208°C, lit.[6] 209–212°C; ^{1}H NMR: δ=9.20 (s, 1H, N*H*), 7.78 (s, 1H, N*H*), 7.28–7.23 (m, 5H, C_6H_5), 5.12 (s, 1H, C*H*), 3.51 (s, 3H, OCH_3), 2.23 (s, 3H, CH_3).

3.1.19. 5-Methoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one, 4s. Mp 190–192°C, lit.[6] 192–194°C; ^{1}H NMR: δ=9.17 (s, 1H, N*H*), 7.68 (s, 1H, N*H*), 7.14–6.83 (m, 4H, C_6H_4), 5.07 (s, 1H, C*H*), 3.70 (s, 3H, $C_6H_5-OCH_3$), 3.51 (s, 3H, OCH_3), 2.23 (s, 3H, CH_3).

3.1.20. 5-Methoxycarbonyl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1*H*)-one, 4t. Mp 204–206°C; ^{1}H NMR: δ=9.18 (s, 1H, N*H*), 7.10 (s, 4H, C_6H_4), 5.08 (s, 1H, C*H*), 3.51 (s, 3H, OCH_3), 2.24 (s, 6H, $C_6H_5-CH_3$, CH_3); ^{13}C NMR: δ=185.9, 152.2, 148.4, 141.8, 136.4, 129.0, 126.1, 99.2, 53.6, 50.7, 20.6, 17.8; IR (KBr): 3175, 1691, 1634 cm^{-1}; MS (70 eV, EI): *m/z* (%): 260 (M, 4), 245 (M$-CH_3$, 8), 201 (M$-CO_2CH_3$, 8), 169 (18), 31 (100); Anal.(%): calcd for $C_{14}H_{16}O_3N_2$: C, 64.58; H, 6.20; N, 10.77. Found: C, 64.39; H, 6.12; N, 10.58.

3.1.21. 4-(4-Chlorophenyl)-5-methoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one, 4u. Mp 179–181°C, lit.[6] 179–181°C; ^{1}H NMR: δ=9.28 (s, 1H, N*H*), 7.76 (s, 1H, N*H*), 7.40–7.21 (m, 4H, C_6H_4), 5.12 (s, 1H, C*H*), 3.51 (s, 3H, OCH_3), 2.23 (s, 3H, CH_3).

3.1.22. 5-Methoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one, 4v. Mp 214–215°C, lit.[6] 204–207°C; ^{1}H NMR: δ=9.38 (s, 1H, N*H*), 7.91 (s, 1H, N*H*), 8.22–7.47 (m, 4H, C_6H_4), 5.26 (s, 1H, C*H*), 3.52 (s, 3H, OCH_3), 2.25 (s, 3H, CH_3).

3.1.23. 5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-thione, 4w. Mp 208–210°C; ^{1}H NMR: δ=10.33 (s, 1H, N*H*), 9.64 (s, 1H, N*H*), 7.35–7.19 (m, 5H, C_6H_5), 5.16 (d, *J*=3.5 Hz, 1H, C*H*), 4.00 (q, *J*= 7.0 Hz, 2H, OCH_2CH_3), 2.28 (s, 3H, CH_3), 1.09 (t, *J*= 7.0 Hz, 3H, OCH_2CH_3).

3.1.24. 5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione, 4x. Mp 150–152°C; ^{1}H NMR: δ=10.29 (s, 1H, N*H*), 9.59 (s, 1H, N*H*), 7.14–6.87 (m, 4H, C_6H_4), 5.10 (s, 1H, C*H*), 3.99 (q, *J*=7.0 Hz, 2H, OCH_2CH_3), 3.71 (s, 3H, OCH_3), 2.27 (s, 3H, CH_3), 1.09 (t, *J*=7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR: δ=174.0, 165.2, 158.8, 144.7, 135.8, 127.7, 113.9, 101.1, 59.6, 55.1, 53.5, 17.2, 14.1; IR (KBr): 3250, 1651, 1598, 1561 cm^{-1}; MS (70 eV, EI): *m/z* (%): 306 (M, 82), 277 (M$-C_2H_5$, 80), 32 (100); Anal. (%): calcd for $C_{15}H_{18}O_3N_2S$: C, 58.78; H, 5.93; N, 9.15. Found: C, 58.83; H, 5.77; N, 9.03.

3.1.25. 5-Ethoxycarbonyl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1*H*)-thione, 4y. Mp 192–194°C; ^{1}H NMR: δ=10.27 (s, 1H, N*H*), 9.58 (s, 1H, N*H*), 7.16–7.07 (m, 4H, C_6H_4), 5.12 (s, 1H, C*H*), 4.00 (q, *J*=7.0 Hz, 2H, OCH_2CH_3), 2.27 (s, 3H, $C_6H_5-CH_3$), 2.25 (s, 3H, CH_3), 1.10 (t, *J*=7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR: δ=174.2, 165.2, 144.9, 140.6, 136.9, 129.1, 126.3, 100.9, 59.6, 53.8, 20.7, 17.2, 14.1; IR (KBr): 3255, 1659, 1562 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 290 (M, 100), 261 ($M-C_2H_5$, 77); Anal. (%): calcd for $C_{15}H_{18}O_2N_2S$: C, 62.02; H, 6.25; N, 9.65. Found: C, 62.00; H, 6.47; N, 9.62.

3.1.26. 4-(4-Chlorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione, 4z. Mp 192–194°C; ^{1}H NMR: δ=10.36 (s, 1H, N*H*), 9.65 (s, 1H, N*H*), 7.43–7.19 (m, 4H, C_6H_4), 5.16 (s, 1H, C*H*), 4.00 (q, *J*=6.6 Hz, 2H, OCH_2CH_3), 2.28 (s, 3H, CH_3), 1.08 (t, *J*=6.6 Hz, 3H, OCH_2CH_3); ^{13}C NMR: δ=174.3, 165.0, 145.3, 142.4, 132.3, 128.6, 128.4, 100.4, 59.7, 53.5, 17.2, 14.0; IR (KBr): 3255, 1657, 1560 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 310 (M, 99), 281 ($M-C_2H_5$, 82), 199 (100); Anal. (%): calcd for $C_{14}H_{15}O_2N_2ClS$: C, 54.08; H, 4.87; N, 9.02. Found: C, 54.23; H, 4.71; N, 8.99.

3.1.27. 5-Ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-thione, 4a′. Mp 109–111°C; ^{1}H NMR: δ=10.40 (s, 1H, N*H*), 9.62 (s, 1H, N*H*), 8.25–7.45 (m, 4H, C_6H_4), 5.26 (s, 1H, C*H*), 4.00 (q, *J*=7.1 Hz, 2H, OCH_2CH_3), 2.30 (s, 3H, CH_3), 1.12 (t, *J*=7.1 Hz, 3H, OCH_2CH_3).

3.1.28. 5-Ethoxycarbonyl-6-methyl-4-(2-thienyl)-3,4-dihydropyrimidin-2(1*H*)-thione, 4b′. Mp 215–216°C; ^{1}H NMR: δ=10.46 (s, 1H, N*H*), 9.76 (s, 1H, N*H*), 7.39 (d, *J*=4.1 Hz, 1H, $CH_{ar.}$), 6.95–6.89 (m, 2H, $CH_{ar.}$), 5.41 (s, 1H, C*H*), 4.07 (q, *J*=6.7 Hz, 2H, OCH_2CH_3), 2.26 (s, 3H, CH_3), 1.15 (t, *J*=6.7 Hz, 3H, OCH_2CH_3); ^{13}C NMR: δ=174.7, 164.8, 147.0, 145.3, 126.8, 125.3, 124.2, 101.3, 59.8, 49.4, 17.1, 14.1; IR (KBr): 3245, 1650, 1555 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 282 (M, 99), 253 ($M-C_2H_5$, 50), 109 (100); Anal. (%): calcd for $C_{12}H_{14}O_2N_2S_2$: C, 51.02; H, 5.00; N, 9.93. Found: C, 51.24; H, 4.91; N, 9.71.

3.1.29. 5-Ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione, 4c′. Mp 232–234°C (dec.); ^{1}H NMR: δ=9.95 (s, 1H, N*H*), 8.93 (s, 1H, N*H*), 4.07 (q, *J*=7.0 Hz, 2H, OCH_2CH_3), 3.87 (s, 2H, CH_2), 2.17 (s, 3H, CH_3), 1.18 (t, *J*=7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR (d^6-DMSO+$CDCl_3$): δ=175.8, 165.0, 145.1, 96.0, 59.3, 16.8, 14.2; IR (KBr): 3145, 1701, 1646, 1599 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 200 (M, 99), 271 ($M-C_2H_5$, 100); Anal. (%): calcd for $C_8H_{12}O_2N_2S$: C, 47.96; H, 6.04; N, 13.99. Found: C, 48.12; H, 6.21; N, 14.07.

3.1.30. 13-Ethoxycarbonyl-9-methyl-11-thioxo-8-oxa-10,12-diazatricyclo [7.3.1.0^{2,7}] trideca-2,4,6-triene, 5a. Mp 203–205°C; ^{1}H NMR: δ=9.12 (s, 2H, 2N*H*), 7.20–6.84 (m, 4H, C_6H_4), 4.57 (d, *J*=2.2 Hz, 1H, C*H*), 4.15 (q, *J*=7.0 Hz, 2H, OCH_2CH_3), 3.30 (d, *J*=2.2 Hz, 1H, C*H*), 1.77 (s, 3H, CH_3), 1.22 (t, *J*=7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR: δ=176.6, 167.9, 150.5, 129.7, 128.6, 123.8, 121.0, 116.5, 81.5, 60.9, 48.3, 42.5, 23.5, 14.1; IR (KBr): 3367, 3171, 3086, 1730, 1590, 1565 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 292 (M, 100), 263 ($M-C_2H_5$, 67), 219 ($M-CO_2C_2H_5$, 51), 199 (71); Anal.(%): calcd for $C_{14}H_{16}O_3N_2S$: C, 57.49; H, 5.52; N, 9.59. Found: C, 57.71; H, 5.64; N, 9.38.

3.1.31. 13-Ethoxycarbonyl-9-methyl-11-oxo-8-oxa-10,12-diazatricyclo [7.3.1.0^{2,7}] trideca-2,4,6-triene, 5b. Mp 200–202°C; ^{1}H NMR: δ=7.61 (s, 1H, N*H*), 7.21–6.75 (m, 4H, C_6H_4), 4.46 (d, *J*=2.1 Hz, 1H, C*H*), 4.15 (q, *J*=7.0 Hz, 2H, OCH_2CH_3), 3.25 (d, *J*=2.1 Hz, 1H, C*H*), 1.73 (s, 3H, CH_3), 1.22 (t, *J*=7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR: δ=168.5, 154.9, 150.7, 129.5, 128.7, 125.5, 120.7, 116.7, 83.2, 60.7, 47.8, 44.1, 24.1, 14.1; IR (KBr): 3220, 3082, 1749, 1689 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 276 (M, 35), 247 ($M-C_2H_5$, 73), 203 ($M-CO_2C_2H_5$, 61), 183 (100); Anal. (%): calcd for $C_{14}H_{16}O_4N_2$: C, 60.84; H, 5.84; N, 10.14. Found: C, 60.77; H, 5.90; N, 10.19.

3.1.32. 13-Methoxycarbonyl-9-methyl-11-oxo-8-oxa-10,12-diazatricyclo [7.3.1.0^{2,7}] trideca-2,4,6-triene, 5c. Mp 195–197°C; ^{1}H NMR: δ=7.60 (s, 1H, N*H*), 7.21–6.74 (m, 4H, C_6H_4), 4.46 (d, *J*=2.4 Hz, 1H, C*H*), 3.68 (s, 3H, OCH_3), 3.28 (d, *J*=2.4 Hz, 1H, C*H*), 1.72 (s, 3H, CH_3); ^{13}C NMR: δ=169.0, 154.6, 150.7, 129.5, 128.8, 125.4, 120.7, 116.7, 83.2, 52.1, 47.7, 44.0, 24.1; IR (KBr): 3228, 3085, 1750, 1698 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 262 (M, 36), 247 ($M-CH_3$, 38), 203 ($M-CO_2CH_3$, 46), 169 (100); Anal. (%): calcd for $C_{13}H_{14}O_4N_2$: C, 59.51; H, 5.38; N, 10.69. Found: C, 59.48; H, 5.21; N, 10.77.

3.1.33. The isomerization lapachol–lapachones. Lapachol (193 mg, 0.79 mmol) was added to a stirred solution of $InBr_3$ (282 mg, 0.79 mmol) in CH_2Cl_2. After 24 h, the reaction was quenched with 10 mL of water and extracted with CH_2Cl_2 (2×10 mL). The extract was dried (Na_2SO_4), filtered and evaporated to dryness. The residue was separated by column chromatography on silica gel (hexane–acetate) to give 27.8 mg (0.11 mmol) of α-lapachone and 139 mg (0.57 mmol) of β-lapachone (total yield 87%, α/β=1:5). α-lapachone: mp: 119–121°C, lit.[17] 117°C; ^{1}H NMR ($CDCl_3$): δ=7.94 (dd, *J*=7.5, 1.2 Hz, 1H, C·$H_{ar.}$), 7.72 (dd, *J*=7.5, 1.2 Hz, 1H, C·$H_{ar.}$), 7.56 (td, *J*=7.5, 1.2 Hz, 1H, C·$H_{ar.}$), 7.42 (td, *J*=7.5, 1.2 Hz, 1H, C·$H_{ar.}$), 2.47 (t, *J*=6.9 Hz, 2H, CH_2), 1.77 (t, *J*=6.9 Hz, 2H, CH_2), 1.39 (s, 6H, CH_3); β-lapachone: mp: 154–155°C, lit.[17] 154°C; ^{1}H NMR ($CDCl_3$): δ=7.90 (m, 2H, C·$H_{ar.}$), 7.54 (m, 2H, C·$H_{ar.}$), 2.50 (t, *J*=6.6 Hz, 2H, CH_2), 1.73 (t, *J*=6.6 Hz, 2H, CH_2), 1.38 (s, 6H, CH_3).

3.2. Supporting information available

Crystallographic data (CIF file) for the crystal structure determination of compound **5a** has been deposited with the Cambridge Crystallographic Data Centre, CCDC no. 171589. Copies may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or web: http://www.ccdc.cam.ac.uk).

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