Indium(III) Chloride-Catalyzed One-Pot Synthesis of Dihydropyrimidinones by a Three-Component Coupling of 1,3-Dicarbonyl Compounds, Aldehydes, and Urea: An Improved Procedure for the Biginelli Reaction

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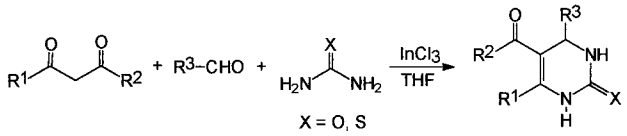
Dihydropyrimidinone derivatives have attracted considerable interest in recent times because of their promising activities as calcium channel blockers, antihypertensive agents and α-1a-antagonists.[1] Moreover, several alkaloids containing the dihydropyrimidine unit have been isolated from marine sources, which also exhibit interesting biological properties.[2] Thus, synthesis of this heterocyclic nucleus is of much current importance. The most simple and straightforward procedure, reported by Biginelli in 1893, involves one-pot condensation of ethyl acetoacetate, benzaldehyde and urea under strongly acidic conditions.[3] However, one serious drawback of Biginelli's reaction is low yields in the case of substituted aromatic and aliphatic aldehydes.[4] This has led to the development of multistep strategies that produce somewhat higher overall yields but lack the simplicity of the one-pot, one-step synthesis.[4,5]

The art of performing efficient chemical transformation coupling three or more components in a single operation by a catalytic process avoiding stoichiometric toxic reagents, large amount of solvents and expensive purification technique, represents a fundamental target of the modern organic synthesis.[6] Thus, Biginelli's reaction for the synthesis of dihydropyrimidinone has received renewed interest and several improved procedures have recently been reported,[3b,7] although some of these methods involve strong Lewis acids such as BF_3,[7e] protic acids such as HCl,[7h] AcOH[7e] and additives.[7e] Consequently, there are scopes for further renovation toward milder reaction conditions, variations of substituents in all three components and better yields.

Scheme 1



Recently, indium(III) chloride has emerged as a powerful Lewis catalyst imparting high regio- and chemoselectivity in various chemical transformations.[8] Our own work also found $InCl_3$ to be a very efficient catalyst for two and three component coupling reactions.[9] We wish to report here another remarkable catalytic activity of $InCl_3$ for the one-pot condensation of 1,3-dicarbonyl compound, aldehyde and urea to dihydropyrimidin-2(1*H*)-ones. (Scheme 1)

In a typical general experimental procedure, a solution of β-dicarbonyl compound, an aldehyde and urea in THF was heated under reflux in the presence of a catalytic amount of indium(III) chloride (10 mol %) for a certain period of time as required to complete the reaction (TLC). The reaction mixture was then poured into crushed ice and the solid product separated was filtered and recrystallized.

A wide range of structurally varied β-dicarbonyl compound, aldehyde and urea are coupled together by this procedure to produce the corresponding dihydropyrimidinones. The results are reported in Table 1. Both β-keto ester and β-diketone participated in this reaction readily. A wide variation in alkyl groups of β-dicarbonyl compounds were tolerated in this procedure. A variety of substituted aromatic, aliphatic, and heterocyclic aldehydes have been subjected to this condensation very efficiently. Thiourea has been used with similar success to provide the corresponding dihydropyrimidin-2(1H)-thiones which are also of much interest with regard to biological activity.[3b] Thus, variations in all three compo-

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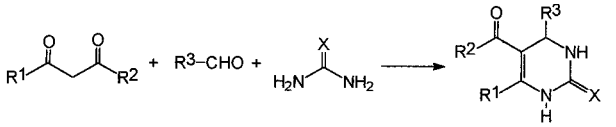
Table 1. $InCl_3$-Catalyzed Synthesis of Dihydropyrimidinones



entry	R^1	R^2	R^3	X	time(h)	yield(%) [a]	ref
1	Me	OEt	Me	O	7	75	10,11
2	Me	OEt	n-Pr	O	7	85	12
3	Me	OEt	i-Pr	O	8	83	12
4	Me	OEt	n-C_6H_{13}	O	8	81	11
5	Me	OEt	Ph	O	7	95	7e
6	Me	OEt	Ph–CH=CH	O	9	90	11
7	Me	OEt	4-(NO_2)–C_6H_4	O	6	93	7e
8	Me	OEt	4-(Cl)–C_6H_4	O	6.5	92	7e
9	Me	OEt	4-(OH)–C_6H_4	O	8	91	7e
10	Me	OEt	4-(OMe)–C_6H_4	O	9	90	7e
11	Me	OEt	3-(OH)–C_6H_4	O	9	88	
12	Me	OEt	3-(OMe)–C_6H_4	O	9	90	
13	Me	OEt	2-(OH)–C_6H_4	O	7	91	11
14	Me	OEt	4-(OH)–C_6H_4	O	9	91	11
15	Me	OMe	Ph	O	7	92	7e
16	Me	OMe	4-(OMe)–C_6H_4	O	9	91	7e
17	Me	OMe	4-(Cl)–C_6H_4	O	6	93	7e
18	Me	OMe	4-(NO_2)–C_6H_4	O	6	91	7e
19	Et	OEt	Ph	O	7	89	7e
20	Et	OEt	4-(OMe)–C_6H_4	O	8	85	7e
21	Et	OEt	4-(Cl)–C_6H_4	O	6	92	7e
22	Et	OEt	4-(NO_2)–C_6H_4	O	6	90	7e
23	Et	OMe	Ph	O	6	95	7e
24	Et	OMe	4-(OMe)–C_6H_4	O	8	91	7e
25	Et	OMe	4-(Cl)–C_6H_4	O	7	92	7e
26	Et	OMe	4-(NO_2)–C_6H_4	O	6	91	7e
27	Ph	OEt	Ph	O	9	84	7e
28	Me	Me	Ph	O	7	94	7g
29	Me	Me	4-(OMe)–C_6H_4	O	9	91	
30	Me	Me	3-(OMe)–C_6H_4	O	9	92	13
31	Me	Me		O	6	93	
32	Me	Me		O	8	90	14
33	Me	Ph	Ph	O	9	88	7g
34	Me	Ph	4-(OMe)–C_6H_4	O	9	90	15
35	Me	OEt	Ph	S	9	91	7b
36	Me	OEt	3-(OMe)–C_6H_4	S	9	90	
37	Me	Me	Ph	S	7	92	16
38	Me	Ph	Ph	S	8	90	

[a] Yields refer to pure solid products, properly characterized by mp, spectral (IR, ^1H, ^{13}C NMR), and analytical data.

nents have been accommodated very comfortably. However, under the present reaction conditions β-keto aldehydes do not produce the corresponding dihydropyrimidinones, instead leads to multiple products whose identities are yet to be established.

Use of just 10 mol % of $InCl_3$ in refluxing THF (65−70 °C) is sufficient to push the reaction forward. Higher amount of $InCl_3$ did not improve the result to a great extent. No additive or protic/Lewis acid is necessary in this procedure. The yields are, in general, very high regardless of the structural variations in dicarbonyl compound, aldehyde or urea. The crude products obtained are of high purity (>95% by ^1H NMR). Another important aspect of this procedure is survival of a variety of functional groups such as NO_2, Cl, OH, OMe, and conjugated C−C double bond under the reaction conditions. Presumably, the reaction proceeds by the usual mechanism proposed using Lewis-acids.[7]

In conclusion, the present procedure of the synthesis of dihydropyrimidin-2(1*H*)-ones by indium(III) chloride catalyzed condensation of 1,3-dicarbonyl compound, aldehyde, and urea provides an efficient and much improved modification of Biginelli's reaction. In addition to its simplicity and milder reaction conditions, this method has the ability to tolerate a wide variety of substitutions in all three components which is lacking in existing procedures.[7] Thus, this procedure will offer an easy access to substituted dihydropyrimidin-2(1*H*)-ones and thiones with varied substitution patterns in very high yields. We believe, our procedure will find important applications in the synthesis of dihydropyrimidinones to cater the needs of academia as well as pharmaceutical industries.

Experimental Section

General Methods. Melting points were determined on a glass disk with an electrical bath and are uncorrected. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were run in DMSO-d_6 solutions. IR spectra were taken as KBr plates. Tetrahydrofuran (THF) was distilled over potassium−benzophenone immediately before use. Indium(III) chloride was purchased from Aldrich and was used as such. 1,3-Dicarbonyl compounds, aldehydes urea and thiourea were all commercial materials. All liquid reagents were distilled before use.

General Procedure for the Synthesis of Dihydropyrimidiones. Representative Procedure for 5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (Entry 5). A solution of ethyl acetoacetate (260 mg, 2 mmol), benzaldehyde (212 mg, 2 mmol) and urea (156 mg, 2.6 mmol) in THF (5 mL) was heated under reflux (65−70 °C) in the presence of indium(III) chloride (44 mg, 10 mol %) for 7 h (TLC) under nitrogen. The reaction mixture, after being cooled to room temperature was poured into crushed ice (20 g) and stirred for 5−10 min. The solid separated was filtered under suction (water aspirator), washed with ice-cold water (20 mL) and then recrystallized from hot ethanol to afford pure product (494 mg, 95%), mp 202−203 °C (lit.[7e] mp 202−204 °C).

This procedure was followed for the preparation of all the dihydropyrimidinones and thiones listed in Table 1. The known compounds have been identified by comparison of spectral data (IR, ^1H NMR, and ^{13}C NMR) and mp with those reported. The mp, spectral, and analytical data of the new compounds have been presented below in order of their entries.

5-Ethoxycarbonyl-4-(3-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (entry 11): mp 164−166 °C; IR 3348, 3247, 1728, 1704, 1681 cm^{-1}; ^1H NMR δ 9.33 (s, 1H), 9.14 (s, 1H), 7.67 (s, 1H), 7.07 (t, J = 7.8 Hz, 1H), 6.63 (m, 3H), 5.05 (d, J = 3 Hz, 1H), 4.01 (q, J = 6.9 Hz, 2H), 2.22 (s, 3H), 1.09 (t, J = 6.9 Hz, 3H); ^{13}C NMR δ 165.7, 157.7, 152.9, 148.1, 146.6, 129.6, 117.2, 114.5, 113.4, 99.7, 59.5, 54.1, 18.1, 14.5. Anal. Calcd

for $C_{14}H_{16}N_2O_4$; C, 60.86; H, 5.84; N, 10.14. Found: C, 60.71; H, 5.69; N, 10.01.

5-Ethoxycarbonyl-4-(3-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (entry 12): mp 207−208 °C; IR 3242, 1701, 1651, 1598 cm^{-1}; ^1H NMR δ 9.17 (s, 1H), 7.70 (s, 1H), 7.23 (t, J = 7.8 Hz, 1H), 6.79 (m, 3H), 5.09 (d, J = 2.7 Hz, 1H), 3.97 (q, J = 6.9 Hz, 2H), 3.70 (s, 3H), 2.22 (s, 3H), 1.09 (t, J = 6.9 Hz, 3H); ^{13}C NMR δ 165.7, 159.5, 152.5, 148.8, 146.6, 129.9, 118.5, 112.7, 102.6, 99.4, 59.5, 55.3, 54.6, 18.1, 14.4. Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65. Found: C, 61.89; H, 6.18; N, 9.49.

5-Acetyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (entry 29): mp 166−168 °C; IR 3230, 1714, 1699, 1596 cm^{-1}; ^1H NMR δ 9.1 (s, 1H), 7.76 (s, 1H), 7.16 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 5.20 (d, J = 3 Hz, 1H), 3.70 (s, 3H), 2.26 (s, 3H), 2.06 (s, 3H); ^{13}C NMR δ 194.7, 158.8, 152.5, 148.1, 136.7, 128.0 (2), 114.2 (2), 109.6, 55.4, 53.7, 30.5, 19.2. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.39; H, 6.01; N, 10.67.

5-Acetyl-4-(3-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (entry 30): mp 228−230 °C; IR 3340, 1714, 1678, 1598 cm^{-1}; ^1H NMR δ 9.16 (s, 1H), 7.80 (s, 1H), 7.22 (t, J = 7.8 Hz, 1H), 6.81 (m, 3H), 5.22 (d, J = 3.3 Hz, 1H), 3.70 (s, 3H), 2.26 (s, 3H), 2.07 (s, 3H); ^{13}C NMR δ 194.6, 159.7, 152.6, 148.5, 146.0, 130.0, 118.7, 113.6, 112.5, 109.7, 55.3, 54.0, 30.6, 19.2. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.42; H, 5.97; N, 10.68.

5-Acetyl-6-methyl-4(2-pyridinyl)-3,4-dihydropyrimidin-2(1*H*)-one (entry 31): mp 224−225 °C; IR 3290, 1712, 1679, 1587 cm^{-1}; ^1H NMR δ 9.13 (s, 1H), 8.47 (m, 1H), 7.71 (m, 2H), 7.23 (m, 2H), 5.31 (d, J = 3.3 Hz, 1H), 2.21 (s, 3H), 2.17 (s, 3H); ^{13}C NMR δ 194.7, 162.7, 152.8, 149.5, 148.3, 137.2, 122.9, 121.0, 109.4, 56.0, 30.7, 19.2. Anal. Calcd for $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.67; N, 18.17. Found: C, 62.01; H, 5.59; N, 17.99.

5-Acetyl-4-(2-furfuryl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (entry 32): mp 210−212 °C; IR 3278, 1716, 1681, 1591 cm^{-1}; ^1H NMR δ 9.21 (s, 1H), 7.82 (s, 1H), 7.53 (s, 1H), 6.33 (s, 1H), 6.10 (d, J = 2.7 Hz, 1H), 5.30 (d, J = 2.7 Hz, 1H), 2.22 (s, 3H), 2.14 (s, 3H); ^{13}C NMR δ 194.1, 156.2, 152.8, 149.1, 142.6, 110.6, 107.5, 105.9, 48.1, 30.3, 19.2. Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.81; H, 5.38; N, 12.59.

5-Benzoyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (entry 34): mp 218−219 °C; IR 3282, 1706, 1674, 1598 cm^{-1}; ^1H NMR δ 9.14 (s, 1H), 7.73 (s, 1H), 7.49 (m, 5H), 7.12 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 5.26 (d, J = 2.4 Hz, 1H), 3.71 (s, 3H), 1.67 (s, 3H); ^{13}C NMR δ 194.7, 158.7, 152.5, 145.3, 141.3, 136.7, 131.7, 128.9 (2), 128.0 (2), 127.7 (2), 114.1 (2), 110.0, 55.3, 55.0, 18.7. Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.58; H, 5.52; N, 8.55.

5-Ethoxycarbonyl-4-(3-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione (entry 36): mp 150−152 °C; IR 3157, 3122, 1710, 1651, 1596 cm^{-1}; ^1H NMR δ 10.37 (s, 1H), 9.71 (s, 1H), 7.27 (t, J = 9 Hz, 1H), 6.84 (m, 3H), 5.90 (s, 1H), 4.03 (q, J = 6 Hz, 2H), 3.73 (s, 3H), 2.30 (s, 3H), 1.12 (t, J = 6 Hz, 3H); ^{13}C NMR δ 174.3, 165.4, 159.6, 145.3, 145.1, 130.1, 118.7, 112.8 (2), 101.1, 60.0, 55.3, 54.2, 17.5, 14.3. Anal. Calcd for $C_{15}H_{18}N_2O_3S$: C, 58.80; H, 5.92; N, 9.14. Found: C, 58.62; H, 5.81; N, 9.05.

5-Acetyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-thione (entry 37): mp 220−222 °C; IR 3282, 1615, 1575 cm^{-1}; ^1H NMR δ 10.06 (s, 1H), 9.53 (s, 1H), 7.04 (m, 5H), 5.07 (s, 1H), 2.01 (s, 3H), 1.92 (s, 3H); ^{13}C NMR δ 195.1, 174.4, 144.9, 143.2, 129.0 (2), 128.0, 126.9 (2), 110.8, 54.1, 30.8, 18.6. Anal. Calcd for $C_{13}H_{14}N_2OS$: C, 63.39; H, 5.73; N, 11.37. Found: C, 63.18; H, 5.61; N, 11.28.

5-Benzoyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-thione (entry 38): mp 228−230 °C; IR 3427, 1666, 1624, 1558 cm^{-1}; ^1H NMR δ 10.35 (s, 1H), 9.69 (s, 1H), 7.44 (m, 10H), 5.31 (d, J = 3 Hz, 1H), 1.75 (s, 3H); ^{13}C NMR δ 194.9, 174.6, 143.3, 141.9, 140.4, 132.2 (2), 129.0 (2), 128.9 (2), 128.0 (2), 126.6 (2), 110.0, 55.7, 18.2. Anal. Calcd for $C_{18}H_{16}N_2OS$: C, 70.10; H, 5.23; N, 9.08. Found: C, 69.89; H, 5.11; N, 8.91.

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