



Calcium fluoride: an efficient and reusable catalyst for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and their corresponding 2(1*H*)thione: an improved high yielding protocol for the Biginelli reaction

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ABSTRACT

A simple and effective synthesis of 3,4-dihydropyrimidinone derivatives from aldehydes, 1,3-dicarbonyl compounds, and urea/thiourea in ethanol by using calcium fluoride as catalyst has been described. Compared with classical Biginelli reaction conditions, this new method has the advantage of excellent yields and shorter reaction times. Also, the catalyst can be reused without any reduction in efficiency.

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In the past decade, dihydropyrimidinones (DHPMs) and their derivatives have attracted considerable interest because they exhibit promising activities as calcium channel blockers, antihypertensive agents, and α -1a-antagonists and neuropeptide Y (NPY) antagonists.¹ Furthermore, several bioactive isolated marine alkaloids were also found to contain a 2-amino-1,4-dihydropyrimidinone-5-carboxylate core.² Most notably among them are the batzalladine alkaloids, which have been found to be potent HIV-gp-120-CD4 inhibitors.³ Their derivatives exhibit a wide spectrum of biological effects including antifungal, antiviral, anticancer, antibacterial, anti-inflammatory, and antihypertensive effects.⁴ Thus, a synthesis of this heterocyclic nucleus has been of much importance in current years. The simple and direct method, originally reported by Biginelli,⁵ for the synthesis of dihydropyrimidinones often suffers from low yields of products in the case of substituted aromatic and aliphatic aldehydes.⁶ This has led to the recent disclosure of several one-pot methodologies for the synthesis of DHPM derivatives involving the use of a number of catalysts such as ZrCl_4 ,⁷ $\text{CuCl}_2 \cdot 2\text{H}_2\text{O} \cdot \text{HCl}$,⁸ LiBr ,⁹ LaCl_3 -graphite,¹⁰ InBr_3 ,¹¹ GaX_3 ,¹² ZnBr_2 ,¹³ 1,1,3,3-tetramethylguanidinium trifluoroacetate,¹⁴ $\text{Cu}(\text{OTf})_2$,¹⁵ [bmim] BF_4 -immobilized $\text{Cu}(\text{II})$ acetylacetonate,¹⁶ and [bmim] $[\text{FeCl}_4]$.¹⁷ However, many of these methods also suffer from drawbacks, such as the involvement of expensive reagents. Though the reusability of the catalyst has been claimed in three cases,^{15–17} it has been demonstrated only for $\text{Cu}(\text{OTf})_2$.¹⁵ We report that CaF_2 , which is cheaper than all these catalysts, can be used as an effective reusable catalyst for the Biginelli reaction (Scheme 1).

The model reaction of ethyl acetoacetate **2a** (10 mmol), benzaldehyde **1a** (10 mmol), urea **3** (15 mmol), and CaF_2 (1 mmol, 10 mol %) in EtOH (20 ml) gave the product in 98% yield (Scheme

1). The reusability of the catalyst was next checked by the same model reaction four times. The results are summarized in Table 1. It is seen that the efficiency of the catalyst is not reduced on reuse.

The catalyst was used in 16 reactions and the results are summarized in Table 2.¹⁸ It is seen that several aromatic aldehydes carrying either electron-releasing or electron-withdrawing substituents in the *ortho* and *para* positions afford high yields of the products. Another important feature of this procedure is the survival of a variety of functional groups under the reaction conditions. Thiourea has been used with similar success to provide the corresponding 3,4-dihydropyrimidin-2(1*H*)-thione **4i** which is also of much interest with respect to its biological activity.

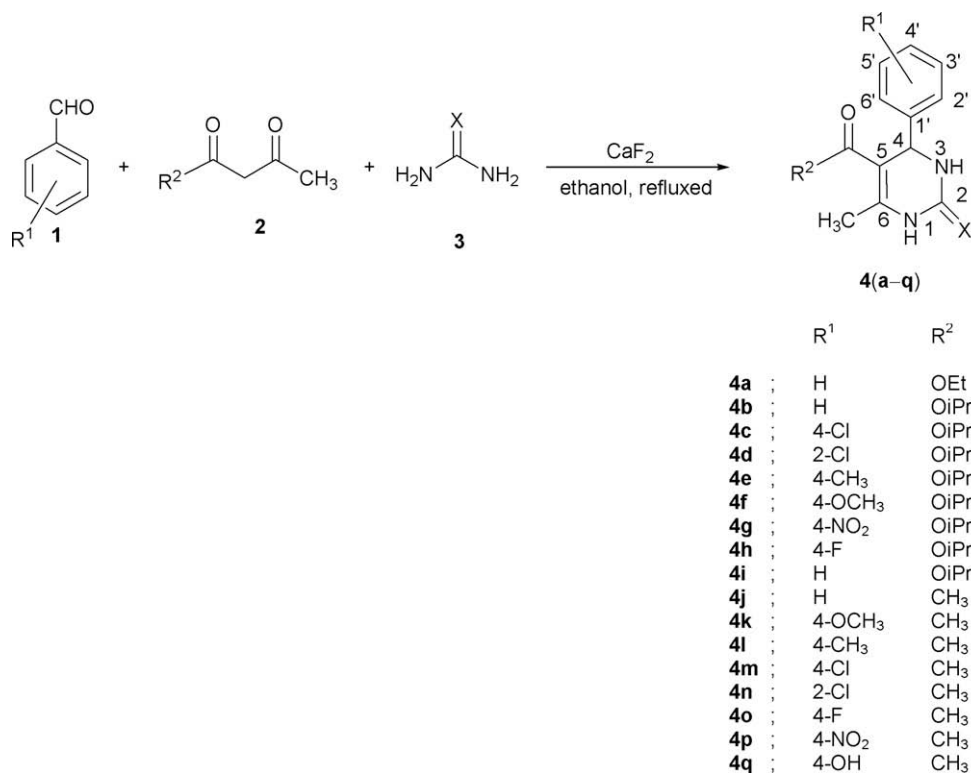
However, the reaction did not give pure product for 3-chlorobenzaldehyde. We have not tried the methods for aliphatic aldehydes.

In all cases, the purity of the product was confirmed by elemental analysis. The structures of the pure products were confirmed by IR, ^1H NMR, and ^{13}C NMR spectral data. In compounds **4b**, **4c**, **4e**, **4i**, **4j**, **4l**, **4m**, **4n**, **4o**, **4p**, and **4q**, the benzylic proton appeared as a doublet around 5.2 ppm. This is due to its coupling with the adjacent NH (H-3) proton. In compounds **4a**, **4d**, **4f**, **4g**, **4h**, and **4k** the benzylic proton appeared as a broad singlet due to the poor resolution of the coupling with the NH proton. However, in all cases, the NH (H-3) proton appeared as a broad singlet around 5.5 ppm due to poor resolution. In compounds **4b–h**, two separate doublets appeared for the methyl groups of the isopropyl groups since they are diastereotopic. Also, in the ^{13}C NMR spectra of these compounds, two signals were observed for the methyl carbons of the isopropyl group. The assignment of ^1H NMR and ^{13}C NMR signals was confirmed using the HSQC spectrum for **4c** and HSQC and HMBC spectra for **4j**.

This study shows that CaF_2 is an excellent catalyst for the Biginelli reaction.

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**Scheme 1.** Synthesis of DHPMs catalyzed by CaF₂.**Table 1**
Yields of dihydropyrimidin-2(1H)-one **4a** for successive runs

Run	Reaction time (h)	Catalyst (in mol %)	Yield (%)	Mp (°C)
1	2	10	98	202–203
2	2	10	98	201–202
3	2	10	94	202–203
4	2	10	94	203–204

Table 2
CaF₂-catalyzed synthesis of different 3,4-dihydropyrimidinones (**4a–q**)

Compound	R ¹	R ²	X	Time (h)	Yield (%)	Mp (°C)
4a	H	OEt	O	2	98	202–203
4b	H	OiPr	O	1.30	98	223–224
4c	4-Cl	OiPr	O	2	98	231–232
4d	2-Cl	OiPr	O	1.30	96	224–226
4e	4-CH ₃	OiPr	O	2	94	237–238
4f	4-OCH ₃	OiPr	O	1.30	98	243–245
4g	4-NO ₂	OiPr	O	3	96	196–197
4h	4-F	OiPr	O	2	96	164–165
4i	H	OiPr	S	2	90	203–204
4j	H	CH ₃	O	2	96	264–265
4k	4-OCH ₃	CH ₃	O	2	98	201–202
4l	4-CH ₃	CH ₃	O	2	90	256–257
4m	4-Cl	CH ₃	O	3	96	258–260
4n	2-Cl	CH ₃	O	2	92	282–283
4o	4-F	CH ₃	O	2	90	260–261
4p	4-NO ₂	CH ₃	O	3	90	Above 400 °C
4q	4-OH	CH ₃	O	2	92	236–238

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- Preparation and characterization of DHPMs*: A mixture of aldehyde (10 mmol), 1,3-dicarbonyl compound (10 mmol), urea (15 mmol), CaF₂ (1 mmol, 10 mol %), and EtOH (20 ml), was heated at 40 °C. The progress of the reaction was monitored by TLC. The completion of the reaction was inferred by the absence of the spot for the aromatic aldehyde. After completion of the reaction, the reaction mixture was cooled to room temperature and poured into crushed ice. The crude product containing also the catalyst was collected on a Buchner funnel by filtration. The mixture of the product and the catalyst was digested in methanol (40 ml). The undissolved catalyst was removed by filtration. The crude product was obtained by evaporation of methanol and

further purified by recrystallization from hot ethanol to afford pure dihydropyrimidin-2(1H)-ones. The catalyst could be reused in the next run. All the products were characterized by elemental analyses, IR, ^1H NMR and ^{13}C NMR spectra. For compounds **4a**, **4j**, **4k**, **4m**, and **4n** the observed spectral data were in excellent agreement with those reported.¹⁹ Only for the newly synthesized compounds the spectral and analytical data are given below.

Compound 4b: IR (KBr) cm^{-1} = 3246 and 3119 (N–H str.), 1706 and 1651 (C=O str.); ^1H NMR (DMSO- d_6) δ = 9.11 (s, 1H, H-1), 7.67 (s, 1H, H-3), 7.32–7.21 (m, 5H, Ar-H), 5.11 (d, 1H, J = 4 Hz, H-4), 4.79 (m, 1H, CH of iPr), 1.14 and 0.96 (d, 3H, J = 4 Hz, CH_3 of iPr), 2.23 (s, 3H, CH_3 at C-6); ^{13}C NMR (DMSO- d_6) δ = 164.7 (CO of the ester), 152.0 (C-6), 148.0 (C-2), 144.9 (C-1'), 128.2, 127.1 and 126.2 (other aromatic carbons), 99.4 (C-5), 66.2 (CH of iPr), 54.0 (C-4), 21.7 and 21.3 (CH_3 of iPr), 17.6 (CH_3 at C-6); MS (m/z , %) 275 [(M+1) $^+$], 100], 231 (65), 197 (48), 187 (38). Anal. Calcd for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_3$: C, 65.69; H, 6.56; N, 10.21. Found: C, 65.80; H, 6.58; N, 10.25.

Compound 4c: IR (KBr) cm^{-1} = 3248 and 3120 (N–H str.), 1722 and 1648 (C=O str.); ^1H NMR (DMSO- d_6) δ = 9.10 (s, 1H, H-1), 7.61 (s, 1H, H-3), 7.33–7.26 (m, 4H, Ar-H), 5.20 (d, 1H, J = 4 Hz, H-4), 4.86 (m, 1H, CH of iPr), 1.18 and 1.02 (d, 3H, J = 4 Hz, CH_3 of iPr), 2.28 (s, 3H, CH_3 at C-6); ^{13}C NMR (DMSO- d_6) δ = 164.6 (CO of the ester), 152.2 (C-6), 147.9 (C-2), 143.5 (C-1'), 132.0 (C-4'), 127.9 and 127.8 (other aromatic carbons), 99.2 (C-5), 66.2 (CH of iPr), 53.7 (C-4), 21.6 and 21.3 (CH_3 of iPr), 17.7 (CH_3 at C-6). Anal. Calcd for $\text{C}_{15}\text{H}_{17}\text{N}_2\text{O}_3\text{Cl}$: C, 58.35; H, 5.51; N, 9.07. Found: C, 58.48; H, 5.49; N, 9.05.

Compound 4d: IR (KBr) cm^{-1} = 3246 and 3118 (N–H str.), 1709 and 1649 (C=O str.); ^1H NMR (DMSO- d_6) δ = 9.14 (s, 1H, H-1), 7.87 (s, 1H, H-3), 7.34–7.17 (m, 4H, Ar-H), 5.75 (br s, 1H, H-4), 4.81 (m, 1H, CH of iPr), 1.15 and 0.83 (d, 3H, J = 4 Hz, CH_3 of iPr), 2.36 (s, 3H, CH_3 at C-6); ^{13}C NMR (DMSO- d_6) δ = 164.9 (CO of the ester), 152.2 (C-6), 149.0 (C-2), 141.6 (C-1'), 132.3 (C-4'), 129.4, 128.9, 128.8 and 127.5 (other aromatic carbons), 98.6 (C-5), 66.5 (CH of iPr), 51.9 (C-4), 21.9 and 21.4 (CH_3 of iPr), 18.0 (CH_3 at C-6). Anal. Calcd for $\text{C}_{15}\text{H}_{17}\text{N}_2\text{O}_3\text{Cl}$: C, 58.35; H, 5.51; N, 9.07. Found: C, 58.36; H, 5.52; N, 9.04.

Compound 4e: IR (KBr) cm^{-1} = 3243 and 3117 (N–H str.), 1706 and 1647 (C=O str.); ^1H NMR (DMSO- d_6) δ = 9.03 (s, 1H, H-1), 7.54 (s, 1H, H-3), 7.17–7.06 (m, 4H, Ar-H), 5.17 (d, 1H, J = 4 Hz, H-4), 4.84 (m, 1H, CH of iPr), 1.18 and 1.02 (d, 3H, J = 4 Hz, CH_3 of iPr), 2.28 (s, 3H, CH_3 at C-6), 2.27 (s, 3H, CH_3 at C-4'); ^{13}C NMR (DMSO- d_6) δ = 164.8 (CO of the ester), 152.4 (C-6), 147.2 (C-2), 141.8 (C-1'), 136.1 (C-4'), 128.4 and 126.1 (other aromatic carbons), 99.9 (C-5), 66.1 (CH of iPr), 53.9 (C-4), 21.6 and 21.3 (CH_3 of iPr), 20.6 (CH_3 at C-4'), 17.7 (CH_3 at C-6). Anal. Calcd for $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_3$: C, 66.66; H, 6.94; N, 9.72. Found: C, 66.60; H, 6.93; N, 9.70.

Compound 4f: IR (KBr) cm^{-1} = 3243 and 3114 (N–H str.), 1702 and 1649 (C=O str.); ^1H NMR (DMSO- d_6) δ = 8.93 (s, 1H, H-1), 7.83 (s, 1H, H-3), 7.34–6.79 (m, 4H, Ar-H), 5.21 (br s, 1H, H-4), 4.88 (m, 1H, CH of iPr), 1.19 and 1.03 (d, 3H, J = 4 Hz, CH_3 of iPr), 2.29 (s, 3H, CH_3 at C-6), 3.76 (s, 3H, OCH_3 at C-4'); ^{13}C NMR (DMSO- d_6) δ = 164.8 (CO of the ester), 158.2 (C-4'), 152.4 (C-6), 147.0 (C-2), 136.9 (C-1'), 127.4 and 113.0 (other aromatic carbons), 100.1 (C-5), 66.1 (CH of iPr), 54.7 (C-4), 53.8 (OCH_3 at C-4'), 21.6 and 21.3 (CH_3 of iPr), 17.7 (CH_3 at C-6). Anal. Calcd for $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_4$: C, 63.15; H, 6.57; N, 9.21. Found: C, 62.91; H, 6.59; N, 9.24.

Compound 4g: IR (KBr) cm^{-1} = 3246 and 3122 (N–H str.), 1703 and 1645 (C=O str.); ^1H NMR (DMSO- d_6) δ = 9.27 (s, 1H, H-1), 8.19 (d, 2H, J = 8 Hz, Ar-H), 7.86 (s, 1H, H-3), 7.46 (d, 2H, J = 8 Hz, Ar-H), 5.36 (br s, 1H, H-4), 4.87 (m, 1H, CH of iPr), 1.20 and 1.03 (d, 3H, J = 4 Hz, CH_3 of iPr), 2.33 (s, 3H, CH_3 at C-6); ^{13}C NMR (DMSO- d_6) δ = 164.9 (CO of the ester), 152.5 (C-4'), 152.2 (C-6); 149.3 (C-2),

147.0 (C-1'), 128.2 and 123.8 (other aromatic carbons), 99.0 (C-5), 67.0 (CH of iPr), 54.2 (C-4), 22.0 and 21.8 (CH_3 of iPr), 18.2 (CH_3 at C-6). Anal. Calcd for $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_5$: C, 56.42; H, 5.32; N, 13.16. Found: C, 56.50; H, 5.33; N, 13.15.

Compound 4h: IR (KBr) cm^{-1} = 3247 and 3120 (N–H str.), 1705 and 1647 (C=O str.); ^1H NMR (DMSO- d_6) δ = 9.00 (s, 1H, H-1), 7.45 (s, 1H, H-3), 7.32–6.96 (m, 4H, Ar-H), 5.25 (br s, 1H, H-4), 4.88 (m, 1H, CH of iPr), 1.19 and 1.02 (d, 3H, J = 4 Hz, CH_3 of iPr), 2.31 (s, 3H, CH_3 at C-6); ^{13}C NMR (DMSO- d_6) δ = 164.7 (CO of the ester), 162.7 (C-4'), 152.2 (C-6), 147.5 (C-2), 140.7 (C-1'), 128.0 and 114.4 (other aromatic carbons), 99.6 (C-5), 66.2 (CH of iPr), 53.7 (C-4), 21.6 and 21.2 (CH_3 of iPr), 17.7 (CH_3 at C-6). Anal. Calcd for $\text{C}_{15}\text{H}_{17}\text{N}_2\text{O}_3\text{F}$: C, 61.64; H, 5.82; N, 9.58. Found: C, 61.55; H, 5.83; N, 9.55.

Compound 4i: IR (KBr) cm^{-1} = 3238 and 3134 (N–H str.), 1703 (C=O str.), 1593 (C=S str.); ^1H NMR (DMSO- d_6) δ = 9.92 (s, 1H, H-1), 9.34 (s, 1H, H-3), 7.35–7.25 (m, 5H, Ar-H), 5.29 (d, 1H, J = 4 Hz, H-4), 4.92 (m, 1H, CH of iPr), 1.21 and 1.04 (d, 3H, J = 4 Hz, CH_3 of iPr), 2.36 (s, 3H, CH_3 at C-6); ^{13}C NMR (DMSO- d_6) δ = 174.0 (C=S), 164.6 (CO of the ester), 144.1 (C-6), 143.3 (C-1'), 127.8, 127.2 and 126.4 (other aromatic carbons), 101.3 (C-5), 66.7 (CH of iPr), 54.6 (C-4), 21.5 and 21.1 (CH_3 of iPr), 17.1 (CH_3 at C-6). Anal. Calcd for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$: C, 62.06; H, 6.20; N, 9.65. Found: C, 62.19; H, 6.18; N, 9.64.

Compound 4l: IR (KBr) cm^{-1} = 3229 and 3120 (N–H str.), 1701 and 1619 (C=O str.); ^1H NMR (DMSO- d_6) δ = 9.14 (s, 1H, H-1), 7.77 (s, 1H, H-3), 7.11 (s, 4H, Ar-H), 5.19 (d, 1H, J = 4 Hz, H-4), 2.26 (s, 3H, CH_3 at C-6), 2.24 (s, 3H, CH_3 at C-4'), 2.06 (s, 3H, CH_3CO); ^{13}C NMR (DMSO- d_6) δ = 194.3 (CO), 152.1 (C-6), 147.8 (C-2), 141.3 (C-1'), 136.4 (C-4'), 129.0 and 126.3 (other aromatic carbons), 109.5 (C-5), 53.5 (C-4), 30.1 (CH_3CO), 20.6 (CH_3 at C-4'), 18.8 (CH_3 at C-6). Anal. Calcd for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_2$: C, 68.85; H, 6.55; N, 11.47. Found: C, 69.00; H, 6.53; N, 11.43.

Compound 4o: IR (KBr) cm^{-1} = 3257 and 3153 (N–H str.), 1708 and 1675 (C=O str.); ^1H NMR (DMSO- d_6) δ = 9.11 (s, 1H, H-1), 7.64 (s, 1H, H-3), 7.28–7.33 (m, 4H, Ar-H), 5.35 (d, 1H, J = 4 Hz, H-4), 2.23 (s, 3H, CH_3 at C-6), 2.11 (s, 3H, CH_3CO); ^{13}C NMR (DMSO- d_6) δ = 194.7 (CO), 161.5 (C-4'), 152.5 (C-6), 147.8 (C-2), 139.6 (C-1'), 128.2 and 115 (other aromatic carbons), 109.5 (C-5), 53.5 (C-4), 30.0 (CH_3CO), 19.0 (CH_3 at C-6). Anal. Calcd for $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}_2\text{F}$: C, 62.90; H, 5.24; N, 11.29. Found: C, 62.85; H, 5.23; N, 11.26.

Compound 4p: IR (KBr) cm^{-1} = 3251 and 3120 (N–H str.), 1727 and 1623 (C=O str.); ^1H NMR (DMSO- d_6) δ = 9.38 (s, 1H, H-1), 8.00 (s, 1H, H-3), 8.15 (d, 2H, J = 8 Hz, Ar-H), 7.54 (d, 2H, J = 8 Hz, Ar-H), 5.45 (d, 1H, J = 4 Hz, H-4), 2.35 (s, 3H, CH_3 at C-6), 2.20 (s, 3H, CH_3CO); ^{13}C NMR (DMSO- d_6) δ = 194.2 (CO), 152.6 (C-4'), 151.7 (C-6), 149.3 (C-2), 147 (C-1'), 128.0 and 123.9 (other aromatic carbons), 109.8 (C-5), 53.7 (C-4), 30.9 (CH_3CO), 19.5 (CH_3 at C-6). Anal. Calcd for $\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}_4$: C, 56.72; H, 4.72; N, 15.27. Found: C, 56.80; H, 4.73; N, 15.31.

Compound 4q: IR (KBr) cm^{-1} = 3267 and 3108 (N–H str.), 1699 and 1648 (C=O str.); ^1H NMR (DMSO- d_6) δ = 9.18 (s, 1H, H-1), 8.95 (s, 1H, H-3), 7.41 (d, 2H, J = 8 Hz, Ar-H), 7.01 (d, 2H, J = 8 Hz, Ar-H), 5.14 (d, 1H, J = 4 Hz, H-4), 2.24 (s, 3H, CH_3 at C-6), 1.98 (s, 3H, CH_3CO); ^{13}C NMR (DMSO- d_6) δ = 195.8 (CO), 157.4 (C-4'), 153.2 (C-6), 148.1 (C-2), 135.1 (C-1'), 128.4, 116.0 (other aromatic carbons), 110.2 (C-5), 55.0 (C-4), 30.6 (CH_3CO), 19.7 (CH_3 at C-6). Anal. Calcd for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_3$: C, 63.41; H, 5.69; N, 11.38. Found: C, 63.50; H, 5.68; N, 11.35.

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