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Archives of Applied Science Research, 2012, 4 (4):1716-1722
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-508X
CODEN (USA) AASRC9

Nickel (II) fluoride-catalyzed one-pot synthesis of dihydropyrimidinones under solvent free conditions

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ABSTRACT

NiF_2 is an efficient, inexpensive and readily available catalyst for the three component, one-pot condensation reaction of an aldehyde, 1,3-dicarbonyl compounds and urea/thiourea to afford the corresponding dihydro-pyrimidinones in high yield. The catalyst exhibited remarkable reusable activity.

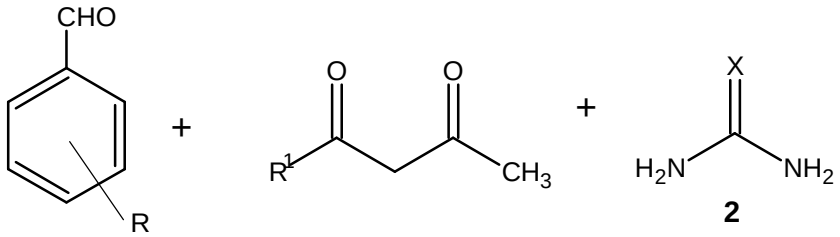
Keywords: Dihydropyrimidinones, Condensation reaction, NiF_2, 1,3 - dicarbonyl compounds, Solvent free**.**

INTRODUCTION

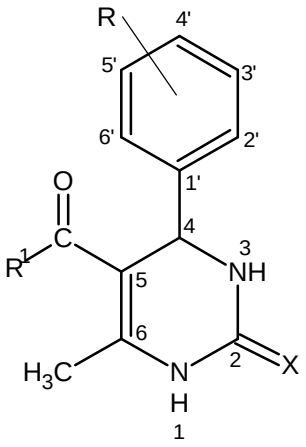
Many dihydropyrimidinones and their derivatives are pharmacologically important as calcium channel blockers, antihypertensive agents and α-1a antagonists[1]. 3,4-Dihydropyrimidinones, denoted as Biginelli compounds and their derivatives are highly important heterocyclic units in the realm of natural and synthetic organic chemistry that possess diverse therapeutic and pharmacological properties, including anti-viral, anti-tumor, anti-bacterial and anti-inflammatory activities [2].

Also, several alkaloids containing the dihydropyrimidine nucleus isolated from marine sources have been found to possess interesting biological activities [3]. Owing to the wide range of pharmacological and biological activities, the synthesis of these compounds has become an important target in current years. The Biginelli reaction, first reported in 1893, is a direct and simple approach for the synthesis of 3,4-dihydropyrimidinones by one-pot cyclocondensation of ethyl acetoacetate, benzaldehyde and urea in the presence of strong acid[4]. However, one serious drawback of this method is the low yield of the product, particularly in case of substituted aromatic and aliphatic aldehydes [5]. This has led to the development of more complex multistep strategies that produce somewhat higher overall yields but lack the simplicity of the one-pot Biginelli protocol [1a],[5],[6].This has led to the recent disclosure of several one-pot methodologies for the synthesis of DHPMs derivatives involving the use of a number catalysts such as $InCl_3$[7], ASA[8], P_2O_5[9], PWA[10], $Yb(OTf)_3$[11], $SrCl_2.6H_2O$-HCl[12], $ZnCl_2$[13], LiBr[14], $Cu(OTf)_2$[15], $CuCl_2.2H_2O$-HCl[16], [bmim] BF_4-immobilized Cu(II)acetylacetonate[17], [bmim]$FeCl_4$[18], 1,1,3,3-tetramethylgaunidinium trifluoroacetate[19], $GaCl_3$[20] , Lemon Juice [21], TBAB[22], etc. However, many of these methods also suffer from drawbacks, such as involvement of expensive reagents, acidic conditions, solvent mediated reactions, longer reaction time, non-reproducible yields and environmental pollution. Apart from these, the heterogeneous catalysts were required in stoichiometric amounts. Furthermore, when thiourea was used low yields of DHPMs were realised. Though the reusability of the catalyst has been claimed in three cases [15],[17],[18] it has been demonstrated only for $Cu(OTf)_2$[15].

Herein we wish to report a simple and efficient method for the synthesis of 3,4-dihydropyrimidinones using nickel fluoride as a reusable and inexpensive catalyst (Scheme 1).



Entry	R	R^1	X
1	H	OC_2H_5	O
2	H	OiPr	O
3	4-Cl	OiPr	O
4	2-Cl	OiPr	O
5	4-CH_3	OiPr	O
6	4-OCH_3	OiPr	O
7	4-NO_2	OiPr	O
8	4-F	OiPr	O
9	H	OiPr	S
10	4-Cl	OiPr	S
11	2-Cl	OiPr	S
12	4-CH_3	OiPr	S
13	4-OCH_3	OiPr	S
14	4-NO_2	OiPr	S
15	4-F	OiPr	S
16	H	CH_3	O
17	4-OCH_3	CH_3	O
18	4-CH_3	CH_3	O
19	4-Cl	CH_3	O
20	2-Cl	CH_3	O
21	4-F	CH_3	O
22	4-NO_2	CH_3	O
23	4-OH	CH_3	O
24	4-$CH(CH_3)_2$	CH_3	O
25	H	CH_3	S
26	4-CH_3	CH_3	S
27	4-Cl	CH_3	S
28	2-Cl	CH_3	S
29	4-F	CH_3	S
30	4-NO_2	CH_3	S
31	4-OCH_3	CH_3	S
32	4-$CH(CH_3)_2$	CH_3	S



1-32

Scheme 1

Synthesis of DHPMs catalyzed by NiF_2

MATERIALS AND METHODS

The course of reaction and the purity were ascertained by performing TLC. Melting points were determined in open capillaries and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 spectrometer operating at 400.13 MHz for ^{1}H and 100.62 MHz for ^{13}C in DMSO-d_6. All NMR measurements were made using 5 mm tubes. For recording ^{1}H NMR spectra, solutions were prepared by dissolving about 10 mg of the compound in 0.5 ml of the solvent. For recording ^{13}C spectra, solutions were prepared by dissolving about 50 mg of the compound in 0.5 ml of the solvent. IR spectra were recorded in KBr discs on an Avatar (300 FT-IR) Thermo Nicolet spectrometer. Elemental analyses were carried out on an Elementar Vario EL III analyzer. Thin layer chromatography was performed on silica gel G (Merck).

General Procedure for the Synthesis of Dihydropyrimidinones. A solution of aldehyde (10 mmol), 1,3-dicarbonyl compound (10 mmol) and urea/thiourea (15 mmol) was heated at 60°C in the presence of nickel(II) fluoride (1 mmol, 10 mol %) for 10 min. (TLC) under solvent free conditions. 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 dihydropyrimidinones. The catalyst could be reused in the next run. All the products were characterized by elemental analyses, IR, ^{1}H NMR and ^{13}C NMR spectra.

The known compounds have been identified by comparison of spectral data (IR, ^{1}H NMR and ^{13}C NMR) and mp with those reported[23],[24]. The mp, spectral and analytical data of the new compounds have been presented below in order of their entries.

Characterization of the DHPMs:

5-Isopropoxycarbonyl-4-(4′-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione: IR (KBr) (cm^{-1}): 3231 and 3119 (N-H str.), 1656 (C=O str.), 1593 (C=S str.); ^{1}H NMR (DMSO-d_6) δ= 10.24 (s, 1H, H-1), 9.64 (s, 1H, H-3), 7.96 (d, 2H, J = 8 Hz, Ar-H), 7.28 (d, 2H, J = 8 Hz, Ar-H), 5.33 (d, 1H, J = 4 Hz, H-4), 4.93 (m, 1H, CH of iPr), 2.37 (s, 3H, CH_3 at C-6), 1.22 and 1.07 (d, 3H, J = 4 Hz, CH_3 of iPr); ^{13}C NMR (DMSO-d_6) δ = 164.4 (CO of the ester), 174.3 (C-2), 144.5 (C-6), 101.3 (C-5), 66.8 (CH of iPr), 53.7 (C-4), 21.6 and 21.3 (CH_3 of iPr), 17.3 (CH_3 at C-6), 142.1 (C-1′), 128.2 (C-2′, C-6′), 128.1 (C-3′, C-5′), 132.5 (C-4′); Anal. Calcd for $C_{15}H_{17}N_2O_2S$ Cl: C, 55.46; H, 5.23; N, 8.62, Found: C, 55.38; H, 5.21; N, 8.63.

5-Isopropoxycarbonyl-4-(2′-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione: IR (KBr) (cm^{-1}): 3231 and 3170 (N-H str.), 1661 (C=O str.), 1581 (C=S str.); ^{1}H NMR (DMSO-d_6) δ= 10.10 (s, 1H, H-1), 8.74 (s, 1H, H-3), 7.30-7.11 (m, 4H, Ar-H), 5.86 (d, 1H, J = 4 Hz, H-4), 4.94 (m, 1H, CH of iPr), 2.34 (s, 3H, CH_3 at C-6), 1.21 and 0.85 (d, 3H, J = 4 Hz, CH_3 of iPr); ^{13}C NMR (DMSO-d_6) δ = 165.7 (CO of the ester), 175.1 (C-2), 145.6 (C-6), 101.0 (C-5), 66.9 (CH of iPr), 52.8 (C-4), 22.0 and 21.4 (CH_3 of iPr), 18.2 (CH_3 at C-6), 139.8 (C-1′), 132.8 (C-2′), 130.2 (C-3′), 130.4 (C-4′), 128.4 (C-5′), 129.5 (C-6′); Anal. Calcd for $C_{15}H_{17}N_2O_2S$ Cl: C, 55.46; H, 5.23; N, 8.62, Found: C, 55.40; H, 5.24; N, 8.64.

5-Isopropoxycarbonyl-4-(4′-methylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione: IR (KBr) (cm^{-1}): 3285 and 3184 (N-H str.), 1654 (C=O str.), 1595 (C=S str.); ^{1}H NMR (DMSO-d_6) δ = 10.14 (s, 1H, H-1), 9.60 (s, 1H, H-3), 7.15 (d, 2H, J = 8 Hz, Ar-H), 7.07 (d, 2H, J = 8 Hz, Ar-H), 5.26 (s, 1H, H-4), 4.96 (m, 1H, CH of iPr), 2.33 (s, 3H, CH_3 at C-6), 2.29 (s, 3H, CH_3 at C-4′) 1.24 and 1.09 (d, 3H, J = 4 Hz, CH_3 of iPr); ^{13}C NMR (DMSO-d_6) δ = 164.9 (CO of the ester), 173.9 (C-2), 144.1 (C-6), 101.2 (C-5), 66.6 (CH of iPr), 53.9 (C-4), 21.6 and 21.2 (CH_3 of iPr), 20.9 (CH_3 at C-4′), 17.2 (CH_3 at C-6), 139.7 (C-1′), 126.5 (C-2′, C-6′), 128.8 (C-3′, C-5′), 136.8 (C-4′); Anal. Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.15; H, 6.57; N, 9.21, Found: C, 63.00; H, 6.59; N, 9.19.

5-Isopropoxycarbonyl-4-(4′-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione: IR (KBr) (cm^{-1}): 3230 and 3156 (N-H str.), 1651 (C=O str.), 1594 (C=S str.); ^{1}H NMR (DMSO-d_6) δ = 9.56 (s, 1H, H-1), 8.98 (s, 1H, H-3), 7.20 (d, 2H, J = 8 Hz, Ar-H), 6.68 (d, 2H, J = 8 Hz, Ar-H), 5.23 (d, 1H, J = 4 Hz, H-4), 4.98 (m, 1H, CH of iPr), 3.78 (s, 3H, OCH_3 at C-4′), 2.28 (s, 3H, CH_3 at C-6), 1.24 and 1.09 (d, 3H, J = 4 Hz, CH_3 of iPr); ^{13}C NMR (DMSO-d_6) δ = 165.9 (CO of the ester), 174.7 (C-2), 144.6 (C-6), 102.3 (C-5), 66.6 (CH of iPr), 54.9 (OCH_3 at C-4′), 53.8 (C-4), 21.5 and 21.2 (CH_3 of iPr), 18.2 (CH_3 at C-6), 135.6 (C-1′), 128.7(C-2′, C-6′), 114.4 (C-3′, C-5′), 159.6 (C-4′); Anal. Calcd for $C_{16}H_{20}N_2O_3S$: C, 60.00; H, 6.25; N, 8.75, Found: C, 60.08; H, 6.27; N, 8.74.

5-Isopropoxycarbonyl-4-(4′-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione: IR (KBr) (cm^{-1}): 3258 and 3176 (N-H str.), 1653 (C=O str.), 1598 (C=S str.); ^{1}H NMR (DMSO-d_6) δ = 10.33 (s, 1H, H-1), 9.74 (s, 1H, H-3), 8.15 (d, 2H, J = 8 Hz, Ar-

H), 7.45 (d, 2H, *J* = 8 Hz, Ar-H), 5.41 (d, 1H, *J* = 4 Hz, H-4), 4.98 (m, 1H, CH of iPr), 2.32 (s, 3H, CH_3 at C-6), 1.25 and 1.10 (d, 3H, *J* = 4 Hz, CH_3 of iPr); ^{13}C NMR (DMSO-d_6) δ = 165.2 (CO of the ester), 175.7 (C-2), 147.5 (C-6), 102.4 (C-5), 67.3 (CH of iPr), 54.5 (C-4), 22.0 and 21.7 (CH_3 of iPr), 18.6 (CH_3 at C-6), 146.2 (C-1′), 128.5 (C-2′, C-6′), 124.2 (C-3′, C-5′), 150.8 (C-4′); Anal. Calcd for $C_{15}H_{17}N_3O_4S$: C, 53.73; H, 5.07; N, 8.35, Found: C, 53.68; H, 5.08; N, 8.37.

5-Isopropoxycarbonyl-4-(4′-fluorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione: IR (KBr) (cm^{-1}): 3231 and 3198 (N-H str.), 1670 (C=O str.), 1599 (C=S str.); ^{1}H NMR (DMSO-d_6) δ = 9.95 (s, 1H, H-1), 9.42 (s, 1H, H-3), 7.21 (d, 2H, *J* = 8 Hz, Ar-H), 6.90 (d, 2H, *J* = 8 Hz, Ar-H), 5.29 (d, 1H, *J* = 4 Hz, H-4), 4.98 (m, 1H, CH of iPr), 2.28 (s, 3H, CH_3 at C-6), 1.25 and 1.09 (d, 3H, *J* = 4 Hz, CH_3 of iPr); ^{13}C NMR (DMSO-d_6) δ = 165.9 (CO of the ester), 174.9 (C-2), 145.2 (C-6), 102.4 (C-5), 66.6 (CH of iPr), 54.9 (C-4), 21.5 and 21.1 (CH_3 of iPr), 18.4 (CH_3 at C-6), 139.4 (C-1′), 129.3 (C-2′, C-6′), 115.8 (C-3′, C-5′), 162.5 (C-4′); Anal. Calcd for $C_{15}H_{17}N_2O_2SF$: C, 58.63; H, 5.53; N, 9.12, Found: C, 58.59; H, 5.55; N, 9.14.

5-Acetyl-4-(4′-isopropylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one: IR (KBr) (cm^{-1}): 3280 and 3145 (N-H str.), 1713 and 1649 (C=O str.); ^{1}H NMR (DMSO-d_6) δ = 8.85 (s, 1H, H-1), 6.34 (s, 1H, H-3), 7.13 (d, 2H, *J* = 8 Hz, Ar-H), 7.06 (d, 2H, *J* = 8 Hz, Ar-H), 5.32 (s, 1H, H-4), 2.77 (m, 1H, CH of iPr), 2.20 (s, 3H, CH_3 at C-6), 2.03 (s, 3H, CH_3 CO), 1.11 (d, 6H, CH_3 of iPr); ^{13}C NMR (DMSO-d_6) δ = 196.3 (CO), 154.9 (C-2), 147.4 (C-6), 111.3 (C-5), 55.8 (C-4), 34.6 (CH of iPr), 30.3 (CH_3 CO), 24.7 (CH_3 of iPr), 19.3 (CH_3 at C-6), 141.1(C-1′), 127.6 (C-2′, C-6′), 127.1 (C-3′, C-5′), 149.6 (C-4′); Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.58; H, 7.35; N, 10.29, Found: C, 70.50; H, 7.37; N, 10.31.

5-Acetyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-thione: IR (KBr) (cm^{-1}): 3288 and 3185 (N-H str.), 1614 (C=O str.) 1579 (C=S str.); ^{1}H NMR (DMSO-d_6) δ = 10.16 (s, 1H, H-1), 9.65 (s, 1H, H-3), 7.30-7.23 (m, 5H, Ar-H), 5.31 (d, 1H, *J* = 4 Hz, H-4), 2.33 (s, 3H, CH_3 at C-6), 2.10 (s, 3H, CH_3CO); ^{13}C NMR (DMSO-d_6) δ = 194.2 (CO), 174.0 (C-2), 144.3 (C-6), 110.0 (C-5), 54.4 (C-4), 30.1 (CH_3 CO), 18.3 (CH_3 at C-6), 142.5 (C-1′), 126.6 (C-2′, C-6′), 128.5 (C-3′, C-5′), 127.6 (C-4′); Anal. Calcd for $C_{13}H_{14}N_2OS$: C, 63.41; H, 5.69; N, 11.38, Found: C, 63.48; H, 5.67; N, 11.40.

5-Acetyl-4-(4′-methylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione: IR (KBr) (cm^{-1}): 3286 and 3187 (N-H str.), 1618 (C=O str.) 1581 (C=S str.); ^{1}H NMR (DMSO-d_6) δ = 10.14 (s, 1H, H-1), 9.60 (s, 1H, H-3), 7.12 (s, 4H, Ar-H), 5.27 (d, 1H, *J* = 4 Hz, H-4), 2.34 (s, 3H, CH_3 at C-6), 2.29 (s, 3H, CH_3 at C-4′), 2.11 (s, 3H, CH_3CO); ^{13}C NMR (DMSO-d_6) δ = 194.7 (CO), 173.8 (C-2), 144.2 (C-6), 110.1 (C-5), 53.9 (C-4), 30.0 (CH_3 CO), 18.2 (CH_3 at C-6), 139.7 (C-1′), 126.5 (C-2′, C-6′), 128.9 (C-3′, C-5′), 136.9 (C-4′), 20.6 (CH_3 at C-4′); Anal. Calcd for $C_{14}H_{16}N_2OS$: C, 64.61; H, 6.15; N, 10.76, Found: C, 64.70; H, 6.16; N, 10.79.

5-Acetyl-4-(4′-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione: IR (KBr) (cm^{-1}): 3236 and 3176 (N-H str.), 1627 (C=O str.), 1567 (C=S str.); ^{1}H NMR (DMSO-d_6) δ = 10.26 (s, 1H, H-1), 9.67 (s, 1H, H-3), 7.95 (d, 2H, *J* = 8 Hz, Ar-H), 7.29 (d, 2H, *J* = 8 Hz, Ar-H), 5.32 (d, 1H, *J* = 4 Hz, H-4), 2.37 (s, 3H, CH_3 at C-6), 2.18 (s, 3H, CH_3 CO); ^{13}C NMR (DMSO-d_6) δ = 194.2 (CO), 174.2 (C-2), 144.6 (C-6), 110.1 (C-5), 53.4 (C-4), 30.2 (CH_3CO), 18.3 (CH_3 at C-6), 141.3 (C-1′), 128.2 (C-2′, C-6′), 128.1 (C-3′, C-5′), 132.6 (C-4′); Anal. Calcd for $C_{13}H_{13}N_2OS$ Cl: C, 55.62; H, 4.63; N, 9.98, Found: C, 55.71; H, 4.62; N, 9.95.

5-Acetyl-4-(2′-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione: IR (KBr) (cm^{-1}): 3234 and 3177 (N-H str.), 1626 (C=O str.), 1567 (C=S str.); ^{1}H NMR (DMSO-d_6) δ = 10.08 (s, 1H, H-1), 8.64 (s, 1H, H-3), 7.30-7.16 (m, 4H, Ar-H), 5.72 (d, 1H, *J* = 4 Hz, H-4), 2.33 (s, 3H, CH_3 at C-6), 2.01 (s, 3H, CH_3 CO); ^{13}C NMR (DMSO-d_6) δ = 195.5 (CO), 175.0 (C-2), 145.6 (C-6), 109.7 (C-5), 52.9 (C-4), 30.5 (CH_3 CO), 19.2 (CH_3 at C-6), 139.7 (C-1′), 132.9 (C-2′), 130.1 (C-3′), 130.2 (C-4′), 128.3 (C-5′), 129.6 (C-6′); Anal. Calcd for $C_{13}H_{13}N_2OS$ Cl: C, 55.62; H, 4.63; N, 9.98, Found: C, 55.70; H, 4.64; N, 10.00.

5-Acetyl-4-(4′-fluorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione: IR (KBr) (cm^{-1}): 3231 and 3197 (N-H str.), 1636 (C=O str.), 1584 (C=S str.); ^{1}H NMR (DMSO-d_6) δ = 9.95 (s, 1H, H-1), 9.43 (s, 1H, H-3), 7.20 (d, 2H, *J* = 8 Hz, Ar-H), 6.92 (d, 2H, *J* = 8 Hz, Ar-H), 5.27 (d, 1H, *J* = 4 Hz, H-4), 2.28 (s, 3H, CH_3 at C-6), 2.05 (s, 3H, CH_3 CO); ^{13}C NMR (DMSO-d_6) δ = 195.7 (CO), 174.8 (C-2), 145.3 (C-6), 111.1 (C-5), 54.5 (C-4), 30.8 (CH_3CO), 19.2 (CH_3 atC-6), 139.3 (C-1′), 129.2 (C-2′, C-6′), 115.9 (C-3′, C-5′), 162.5 (C-4′); Anal. Calcd for $C_{13}H_{13}N_2OSF$: C, 59.09; H, 4.92; N, 10.60, Found: C, 58.98, H, 4.90; N, 10.63.

5-Acetyl-4-(4′-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione: IR (KBr) (cm^{-1}): 3259 and 3178 (N-H str.), 1618 (C=O str.), 1583 (C=S str.); ^{1}H NMR (DMSO-d_6) δ = 10.34 (s, 1H, H-1), 9.74 (s, 1H, H-3), 8.11 (d, 2H, *J* = 8 Hz, Ar-H), 7.45 (d, 2H, *J* = 8 Hz, Ar-H), 5.40 (d, 1H, *J* = 4 Hz, H-4), 2.31 (s, 3H, CH_3 at C-6), 2.19 (s, 3H, CH_3 CO);

^{13}C NMR (DMSO-d_6) δ = 194.8 (CO), 175.5 (C-2), 147.6 (C-6), 111.2 (C-5), 54.3 (C-4), 31.6 (CH_3 CO), 19.4 (CH_3 at C-6), 146.1 (C-1′), 128.3 (C-2′, C-6′), 124.3 (C-3′, C-5′), 150.7 (C-4′); Anal. Calcd for $C_{13}H_{13}N_3O_3S$: C, 53.60; H, 4.46; N, 14.43, Found: C, 53.55; H, 4.47; N, 14.40.

5-Acetyl-4-(4′-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione: IR (KBr) (cm^{-1}): 3231 and 3157 (N-H str.), 1617 (C=O str.), 1578 (C=S str.); ^{1}H NMR (DMSO-d_6) δ = 9.53 (s, 1H, H-1), 8.98 (s, 1H, H-3), 7.12 (d, 2H, *J* = 8 Hz, Ar-H), 6.75 (d, 2H, *J* = 8 Hz, Ar-H), 5.24 (d, 1H, *J* = 4 Hz, H-4), 3.68 (s, 3H, OCH_3 at C-4′), 2.27 (s, 3H, CH_3 at C-6), 2.01 (s, 3H, CH_3 CO); ^{13}C NMR (DMSO-d_6) δ = 195.7 (CO), 174.5 (C-2), 144.6 (C-6), 111.0 (C-5), 55.8 (OCH_3 at C-4′), 55.2 (C-4), 30.8 (CH_3 CO), 19.3 (CH_3 at C-6), 135.6 (C-1′), 128.7 (C-2′, C-6′), 114.6 (C-3′, C-5′), 159.8 (C-4′); Anal. Calcd for $C_{14}H_{16}N_2O_2S$: C, 60.86; H, 5.79; N, 10.14, Found: C, 61.00; H, 5.80; N, 10.16.

5-Acetyl-4-(4′-isopropylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione: IR (KBr) (cm^{-1}): 3291 and 3148 (N-H str.), 1665 (C=O str.), 1594 (C=S str.); ^{1}H NMR (DMSO-d_6) δ = 10.25 (s, 1H, H-1), 9.72 (s, 1H, H-3), 7.21 (d, 2H, *J* = 8 Hz, Ar-H), 7.14 (d, 2H, *J* = 8 Hz, Ar-H), 5.24 (d, 1H, *J* = 4 Hz, H-4), 2.84 (m, 1H, CH of iPr), 2.33 (s, 3H, CH_3 at C-6), 2.15 (s, 3H, CH_3 CO), 1.16 (d, 6H, CH_3 of iPr); ^{13}C NMR (DMSO-d_6) δ = 194.7 (CO), 173.9 (C-2), 144.4 (C-6), 110.4 (C-5), 53.6 (C-4), 33.1 (CH of iPr), 30.5 (CH_3 CO), 23.7 (CH_3 of iPr) 18.3 (CH_3 at C-6), 140.5 (C-1′), 126.5 (C-2′, C-3′, C-5′, C-6′), 147.8 (C-4′); Anal. Calcd for $C_{16}H_{20}N_2OS$: C, 66.66; H, 6.94; N, 9.72, Found: C, 66.60, H, 6.96; N, 9.70.

RESULTS AND DISCUSSION

The model reaction of benzaldehyde (10 mmol), ethyl acetoacetate (10 mmol), urea (15 mmol) and NiF_2 (1 mmol, 10 mol %) was heated at 60°C under solvent free conditions gave the product in 99% yield (Scheme 1). Under these conditions, the yields were significantly raised (90-99% vs for the classical Biginelli method) and the reaction time was shortened from 18 h to 10 min. The most important and salient feature of the reaction is the recyclability of the catalyst and solvent free synthesis. It was observed that the catalyst in the reaction had no effect either on the yield of the product or the quality of the product. Moreover no side products were observed in these reactions. The reusability of the catalyst was next checked by the same model reaction eight times. The results are summarized in Table 1. It is seen that the efficiency of the catalyst is not reduced on reuse.

Table 1. Yields of 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one for successive runs

Run	reaction time (min.)	catalyst (in mol %)	yield (%)	m.p.(°C)
1	10	10	99	201-202
2	10	10	99	202-203
3	10	10	99	201-202
4	10	10	99	201-202
5	10	10	99	202-203
6	10	10	97	202-203
7	10	10	99	201-202
8	10	10	99	201-202

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 2. Both β-diketone and β-ketoester participated in this reaction readily. A variety of substituted aromatic 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[2a]. Aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents afforded high yields of products in high purity. Another important feature of this procedure is the survival of a variety of functional groups such as nitro, hydroxy, halides, etc under the reaction conditions. The advantage of the NiF_2 for this reaction lies in its simplicity. This method utilizes readily available reagents at low cost and also affords high yields of DHPMs in very short reaction times. The mechanism for Biginelli condensation is well explored in the literature [25].

Table 2. Synthesis of dihydropyrimidines catalyzed by NiF_2

Entry	R	R^1	X	yield (%)	m.p. (°C)
1	H	OC_2H_5	O	99	201-202
2	H	OiPr	O	98	224-225
3	4-Cl	OiPr	O	98	231-232
4	2-Cl	OiPr	O	98	223-224
5	4-CH_3	OiPr	O	96	238-239
6	4-OCH_3	OiPr	O	98	242-243
7	4-NO_2	OiPr	O	96	197-198
8	4-F	OiPr	O	98	163-164
9	H	OiPr	S	96	204-205
10	4-Cl	OiPr	S	92	258-259
11	2-Cl	OiPr	S	90	246-247
12	4-CH_3	OiPr	S	94	249-250
13	4-OCH_3	OiPr	S	96	194-195
14	4-NO_2	OiPr	S	90	257-258
15	4-F	OiPr	S	92	239-240
16	H	CH_3	O	98	264-265
17	4-OCH_3	CH_3	O	98	200-201
18	4-CH_3	CH_3	O	94	257-258
19	4-Cl	CH_3	O	96	259-260
20	2-Cl	CH_3	O	94	283-284
21	4-F	CH_3	O	92	259-260
22	4-NO_2	CH_3	O	92	Above 400°C
23	4-OH	CH_3	O	94	237-238
24	4-$CH(CH_3)_2$	CH_3	O	94	180-181
25	H	CH_3	S	96	249-250
26	4-CH_3	CH_3	S	96	251-252
27	4-Cl	CH_3	S	94	257-258
28	2-Cl	CH_3	S	90	209-210
29	4-F	CH_3	S	96	236-237
30	4-NO_2	CH_3	S	92	243-244
31	4-OCH_3	CH_3	S	94	195-196
32	4-$CH(CH_3)_2$	CH_3	S	92	233-234

In all cases, the purity of the product was confirmed by elemental analysis. The structures of the pure products were confirmed by IR, ^{1}H NMR and ^{13}C NMR spectral data. In compounds **2-15,** two separate doublets appeared for the methyl protons of the isopropyl group 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.

CONCLUSION

In summary, this report discloses a new and simple modification of the Biginelli dihydropyrimidinones synthesis. By using NiF_2 as a catalyst and under solvent free reaction conditions, the yields of the one-pot Biginelli reaction can be increased from 20 to 50% to 90-99% while the reaction time was shortened from 18 to 48 h to 10 min. In addition the catalyst can be easily recovered and reused. It not only led to economical automation but also reduces hazardous pollution to achieve environmentally friendly processes. This NiF_2 catalytic one-pot synthesis of dihydropyrimidinones therefore is a simple, high yielding, time saving and environmentally friendly process.

Acknowledgement
Authors are thankful to NMR Research Centre, Indian Institute of Science, Bangalore for recording NMR spectra and CECRI for analyzing the Elemental Analysis.

REFERENCES

[1] (a) K. S Atwal, G. C Rovnyak, B. C.O' Reilly, J. Schwartz, *J. Org. Chem.* **1989,** *54*, 5898 - 5907. (b) C. O. Kappe, W. M. F.Fabian, M.A. Semones, *Tetrahedron* **1997,** *53*, 2803 - 2816.
[2] (a) C. O. Kappe, *Tetrahedron* **1993,** *49*, 6937 - 6963. (b) C. O. Kappe, *Acc. Chem. Res.* **2000,** *33*, 879 - 888. (c) C. O. Kappe, *Eur. J. Med. Chem.* **2000,** *35*, 1043- 1052.
[3] (a) K. S. Atwal, G. C.Rovnyak, S. D. Kimball, D. M.Floyd, S.Moreland, B. N.Swanson, J. Z.Gougoutas, J.Schwartz, K. M.Smillie, M. F. Malley, *J. Med. Chem.* **1990,** *33*, 2629 - 2635. (b) K. S. Atwal, B. N.Swanson, S. E. Unger, D. M.Floyd, S.Moreland, A.Hedberg, B. C. O'Reilly, *J. Med. Chem.* **1991,** *34*, 806 - 811. (c) H. Cho, M.Ueda, K. Shima, A.Mizuno, M.Hayashimatu, Y.Ohnaka, Y.Takechi, M.Hamaguchi, K.Aisaka, T.Hidaka, M.Kawai, M.Takeda, T. Ishihara, K. Funahashi, F. Satah, M.Monta, T. Noguchi, *J. Med. Chem.*, **1989,** *32*, 2399 - 2406.
[4] P. Biginelli, *Gazz. Chim. Ital.* **1893,** *23*, 360 - 413.

[5] J.Barleunga, M..Tomas, A.Ballesteros, L. A. Lopez, *Tetrahedron Lett.* **1989,** *30,* 4573 - 4576.
[6] B. C.O'Reilly, K. S .Atwal,. *Heterocycles* **1987,** *26,* 1185 - 1198.
[7] B. C.Ranu, A.Hajra, U. Jana, *J. Org. Chem.* **2000,** *65,* 6270 - 6272.
[8] S.Besoluk, M.Kucukislamoglu, M.Nebioglu, M.Zengin, M. Arslan, *J. Iran. Chem. Soc.* **2008,** *5,* 62 - 66.
[9] M. B.Deshmukh, P. V. Anbhule, S. D.Jadhav, A. R. Mali, S. S. Jagtap, S. A. Deshmukh, *Indian J. Chem.* **2007,** *46B,* 1545 - 1548.
[10] D. Kumar, B.Gopal Mishra, V. S. Rao, *Indian J. Chem.* **2006,** *45B,* 2325 - 2329.
[11] Y.Ma, C. Qian, L. Wang, M. Yang, *J. Org. Chem.* **2000,** *65,* 3864 - 3868.
[12] M.Nasr-Esfahani, A. Reza Khosropour, *Bull. Koren. Chem. Soc.* **2005,** *21,* 1331 - 1332.
[13] M.A.Pasha, N.Ramachandra Swamy, V. P. Jayashankara, *Indian J. Chem.* **2005,** *44B,* 823 - 826.
[14] G.Maiti, P. Kundu, C. Guin, *Tetrahedron Lett.* **2003,** *44,* 2757 - 2758.
[15]A. S. Paraskar, G. K. Dewkar, A. Sudalai, *Tetrahedron Lett.* **2003,** *44,* 3305 - 3308.
[16] V. N.Pathak, R.Gupta, B. Varshney, *Indian J. Chem.* **2008,** *47B,* 434 - 438.
[17] S. L.Jain, J. K.Joseph, B. Sain, *Catalysis Lett.* **2007,** *115,* 52 - 55.
[18] X.Chen, Y.Peng, *Catalysis Lett.* **2008,** *122,*310 - 313.
[19] A.Shaabani, A. Rahmati, *Catalysis Lett.* **2005,** *100,* 177 - 179.
[20] A.Saini, S.Kumar, J. S. Sandhu, *Indian J. Chem.* **2007,** *46B,* 1886 - 1889.
[21]Suresh Patil, S.D.Jadhav, M.B.Dsehmukh, *Arch. App. Sci. Research*, **2011**,*3*,203 – 208.
[22] T.Kadre, S.R.Jetti, A.Bhatewara, P.Paliwal, S.Jain, *Arch. App. Sci. Research*, **2012**,*4*,988 – 993.
[23] M.Wang, Z. Song, H.Gong, H. Jiang, *Prep. Biochem. Biotechnol.* **2008,** *38,* 105 - 114.
[24] S.Chitra, K. Pandiarajan, *Tetrahedron Lett.* **2009,** *50,* 2222 - 2224.
[25] C. O.Kappe, *J. Org. Chem.* **1997,** *62,* 7201 - 7204