Nano-$TiCl_4.SiO_2$: a Versatile and Efficient Catalyst for Synthesis of Dihydropyrimidones *via* Biginelli Condensation

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ABSTRACT

Nano-$TiCl_4.SiO_2$ has been found to be an extremely efficient catalyst for the preparation of 3,4-dihydropyrimidinones/thiones *via* three-component reactions of an aldehyde, β-ketoester or β-diketone and urea or thiourea under mild conditions. Nano-$TiCl_4.SiO_2$ as a solid Lewis acid has been synthesized by reaction of nano-SiO_2 and $TiCl_4$. The structural characterization of this acid has been studied by FT-IR (ATR), XRD, SEM and TEM. This process was simple and environmentally benign with high to excellent yields. Furthermore, the catalyst could be recovered conveniently and reused for at least three times.

KEYWORDS

Nano-$TiCl_4.SiO_2$, heterogeneous catalyst, multi-component reaction, β-ketoester, β-diketone, urea.

1. Introduction

The Biginelli reaction is an acid-catalyzed, three component, reaction between an aldehyde, *β*-ketoester or *β*-diketone and urea or thiourea. Dihydropyrimidinones (DHPMs) and their derivatives have attracted considerable interest due to their wide spectra of biological activities such as antiviral,[1] antitumor,[2] antibacterial,[3] anti-inflammatory[4] and antihypertensive.[5] The multi-component DHPM-yielding Biginelli reaction was first established in 1893 and was ignored for many years until recently.[6]

Particular enantiomers are progressively more important for drug applications. Chiral detection allows one enantiomer to treat a disease, while another one may be harmfull.[7] An asymmetric carbon exists at the 4-position of the dihydropyrimidone ring and they are generally formulated as racemic mixtures. The absolute configuration in the centre of the molecule can have important biological and pharmacological effects. In many cases chiral dihydropyrimidones have exhibited higher activities or, in the case of enantiomers, a contrary pharmacological activity.[8]

Recently, significant efforts have been made to find new procedures to deliver DHPMs in good yields. A large number of optimized procedures have been reported where most of the protocols employ various catalytic methods in order to synthesize DHPMs. These protocols utilize Lewis acids or metal-based catalysts such as $Ag_3PW_{12}O_{40}$,[9] $LaCl_3.7H_2O$[10] $La(OTf)_3$,[11] $Yb(OTf)_3$,[12] $ZrCl_4$,[13] $BiCl_3$,[14] $Mn(OAc)_3$,[15] $LiClO_4$,[16] H_3BO_3,[17] $CeCl_3/InCl_3$[18], $Al(HSO_4)_3$,[19] $KHSO_4$,[20] ZnI_2,[21] trichloroisocyanuric acid (TCCA),[22] zeolite[23] and HBF_4.[24] However, each method has certain restrictions with regard to scope and reaction conditions; For example, costs of synthesis, unrecoverable catalysts, strong acidic conditions, long reaction times, low yields, difficult work-up and harsh reaction conditions. To avoid these limitations, we have investigated the use of nano-$TiCl_4.SiO_2$.

2. Experimental

2.1. General

The chemicals were obtained form Merck Company and used without any additional purification. The products were characterized by FT-IR (ATR), ^{1}H NMR, and a comparison of their physical properties with those reported in the literature was made. FT-IR (ATR) spectra were recorded on a Bruker, Eqinox 55 spectrometer. A Bruker (DRX-400 Avance) NMR was used to record the ^{1}H NMR spectra. The X-ray diffraction (XRD) patterns of materials were recorded by employing a Philips Xpert MPD diffractometer equipped with a Cu Kα anode (λ = 1.54 Å) in the 2θ range from 10 to 80 °. The SEM of nano particles was determined with a VEGA/TESCAN scanning electron microscope and the TEM photograph was prepared on a Leo 912AB OMEGA microscope.

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2.2. General Method for the Synthesis of 3,4-Dihydropyrimidinones/thiones

A mixture of aldehyde (2 mmol), ethyl acetoacetate/acetylaceton (2 mmol), urea/thiourea (2.5 mmol) and nano-$TiCl_4.SiO_2$ (0.05 g) was heated with stirring at 60 °C for 18 minutes. The progress of the reaction was monitored by TLC (chloroform:petroleum ether, 80:20). After completion of the reaction, the mixture was cooled to room temperature and diluted with acetone. The catalyst was recovered by filtration and washed with acetone (2 × 5 mL). The solvent was evaporated and the crude product recrystallized from 85 % ethanol. All the products were identified by comparison of their physical and spectral data with those of authentic samples.

*5-Ethoxycarbonyl-6-methyl-4-(2-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one* (Table 3, Entry 1)

Yield 90 % (recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 80:20, Rf = 0.4); M.p. 218–219 °C (221 °C)[31], FT-IR: $\bar{\nu}_{max}$ (KBr) = 3367, 3235, 1697, 1644, 1475, 1608, 1580, 1521, 1445, 1360, 1338, 1088, 1220, 783 cm^{-1}.

*5-Ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one* (Table 3, Entry 2)

Yield 95 % (recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 80:20, Rf = 0.4); M.p. 210–211 °C (211 °C)[31]; FT-IR: $\bar{\nu}_{max}$ (KBr) = 3229, 3112, 1725, 1698, 1642, 1597, 1489, 1594, 1518, 1518, 1462, 1374, 1347, 1290, 1084, 1210, 855 cm^{-1}, ^{1}H NMR (500 MHz, DMSO-d_6): 1.10 (t, *J* = 7.0 Hz, 3H), 2.27 (s, 3H), 4.0 (q, *J* = 7.0 Hz, 2H), 5.38 and 5.39 (s, 1H), 7.01 (s, NH), 7.44 (d, *J* = 8.5 Hz, 2H), 8.07 (d, *J* = 8.5 Hz, 2H), 8.86 (s, NH) ppm.

*4-(4-Chlorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-on* (Table 3, Entry 3)

Yield 91 % (recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 80:20, Rf = 0.4); M.p. 211–214 °C (211–213 °C)[30]; FT-IR: $\bar{\nu}_{max}$ (KBr) = 3238, 3116, 1721, 1699, 1645, 1460, 1594, 1577, 1423, 1367, 1289, 1085, 1217, 779, 683 cm^{-1}.

*5-Ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one* (Table 3, Entry 4)

Yield 80 % (recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 80:20, Rf = 0.5); M.p. 201–204 °C (203 °C)[31]; FT-IR: $\bar{\nu}_{max}$ (KBr) = 3237, 3116,1722, 1702, 1647, 1511, 1588, 1583, 1541, 1458, 1367, 1251, 1086, 1218, 1031, 1277, 779 cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d6, ppm): 1.20 (t, J = 7.1 Hz, 3H), 2.35 (s, 3H), 3.80 (s, 3H), 4.10 (q, J = 7.1 Hz, 1H), 4.12 (q, J = 7.1 Hz, 1H), 5.36 and 5.37 (s, 1H), 6.12 (s, NHH), 6.85 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 8.6 Hz, 2H), 8.61 (s, NH) ppm.

*5-Ethoxycarbonyl-4-(3-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one* (Table 3, Entry 5)

Yield 90 % (recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 80:20, Rf = 0.5); M.p. 202–203 °C (205–207 °C)[41] FT-IR: $\bar{\nu}_{max}$ (KBr) = 3237, 3108, 1699, 1650, 1494, 1598, 1550, 1522, 1460, 1375, 1275, 1257, 1091, 1223, 1038, 697, 772, 862 cm^{-1}.

*5-Ethoxycarbonyl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1*H*)-one* (Table 3, Entry 6)

Yield 89 % (recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 80:20, Rf = 0.3); M.p. 215–218 °C (214 °C)[31]; FT-IR: $\bar{\nu}_{max}$ (KBr) = 3233, 3114, 1724, 1701, 1646, 1514, 1586, 1580, 1519, 1460, 1370, 1286, 1086, 1218, 777 cm^{-1}.

*5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one* (Table 3, Entry 7)

Yield 86 % (recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 80:20, Rf = 0.3); M.p. 205–206 °C (204 °C)[31]; FT-IR: $\bar{\nu}_{max}$ (KBr) = 3240, 3122, 1722, 1698, 1645, 1486, 1600, 1599, 1586, 1464, 1340, 1271, 1088, 1218, 699, 757 cm^{-1}, ^{1}H NMR (500 MHz, DMSO-d6): 1.19 (t, J = 7.1 Hz, 3H), 2.36 (s, 3H), 4.10 (q, J = 7.1 Hz, 1H), 4.11 (q, J = 7.1 Hz, 1H), 5.421 and 5.426 (s, 1H), 6.07 (s, NH), 7.27–7.34 (m, 5H), 8.52 (s, NH) ppm.

*5-Ethoxycarbonyl-6-methyl-4-phenethyl-3,4-dihydropyrimidin-2(1*H*)-one* (Table 3, Entry 8)

Yield 89 % (Recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 80:20, Rf = 0.27); M.p. 155–157 °C (252–153 °C)[40]; FT-IR: $\bar{\nu}_{max}$ (KBr) = 3242, 3200, 1722, 1702, 1650, 1494, 1605, 1552, 1454, 1360, 1089, 1287, 1223, 695, 773 cm^{-1}, ^{1}H NMR (500 MHz, DMSO-d6): 1.28 (t, J = 7.1 Hz, 3H), 1.93 (m, 2H), 2.32 (s, 3H), 2.69 (m, 1H), 2.80 (m, 1H), 4.19 (q, J = 7.1 Hz, 1H), 4.20 (q, J = 7.1 Hz, 1H), 4.37 and 4.38 (t, 1H), 6.15 (s, NH), 7.20 (m, 3H), 7.30 (t, J = 5.6 Hz, 2H), 8.35 (s, NH) ppm.

*5-Methoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-thione* (Table 3, Entry 9)

Yield 80 % (recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 70:30, Rf = 0.3); M.p. 181–182 °C (184 °C)[37]; FT-IR: $\bar{\nu}_{max}$ (KBr) = 3277, 3178, 1613, 1453, 1613, 1525, 1385, 1362, 1330, 1116, 694, 774 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d6, ppm): 2.06 and 2.08 (s, 3H), 2.32 (s, 3H), 5.36 and 5.37 (s, 1H), 7.20–7.29 (m, 5H), 8.64 (s, NH), 9.18 (s, NH) ppm.

*5-Ethoxycarbonyl-6-methyl-4-styryl-3,4-dihydropyrimidin-2(1*H*)-one* (Table 3, Entry 10)

Yield 92 % (recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 80:20, Rf = 0.31); M.p. 229–230 °C (232–233 °C)[39]; FT-IR: $\bar{\nu}_{max}$ (KBr) = 3239, 3113, 1721, 1698, 1650, 1486, 1602, 1583, 1463, 1366, 1286, 1089, 1223, 692, 755 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d6) 1.31 (t, J = 7.1 Hz, 3H), 2.33 (s, 3H), 4.21 (q, J = 7.1 Hz, 1H), 4.23 (q, J = 7.1 Hz, 1H), 5.00 and 5.02 (s, 1H), 5.66 (s, NH), 6.23 (dd, J = 15.8 and 6.4 Hz, 1H), 6.51 (d, J = 15.8 Hz, 1H), 7.24 (t, J = 7.4 Hz, 1H), 7.31 (t, J = 7.4 Hz, 2H), 7.37 (d, J = 7.4 Hz, 2H), 7.6 (s, NH) ppm.

*4-(2-Chloro-5-nitrophenyl)-5-ethoxycarbonyl-6-phenyl-3,4-dihydropyrimidin-2(1*H*)-thione* (Table 3, Entry 11)

Yield 78 % (recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 70:30, Rf = 0.55); M.p. 236–238 °C (239 °C)[38]; FT-IR: $\bar{\nu}_{max}$ (KBr) = 3257, 1666, 1494, 1602, 1551, 1525, 1440, 1398, 1375, 1344, 1344, 1063, 1199, 1142, 698 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d6) 0.84 (t, J = 7.1 Hz, 3H), 3.87 (q, J = 7.1 Hz, 2H), 6.05 and 6.06 (s, 1H), 7.49–7.54 (m, 5H), 7.57 (s, NH), 7.67 (d, J = 8.7 Hz, 1H), 8.0 (s, NH), 8.20 (dd, J = 8.7 and 2.6 Hz, 1H), 8.35 (d, J = 2.6 Hz, 1H) ppm.

*4-(4-N,N-Dimethylaniline)-5-(ethoxycarbonyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione* (Table 3, Entry 12)

Yield 89 % (Recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 70:30, Rf = 0.33); M.p. 209–210 °C (not found); FT-IR: $\bar{\nu}_{max}$ (KBr) = 3273, 3160, 1701, 1447, 1596, 1523, 1473, 1411, 1361, 1314, 1314, 1091, 1278, 1124, 814 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d6) 1.13 (t, J = 7.1 Hz, 3H), 2.27 (s, 3H), 2.87 (s, 6H), 4.0 (q, J = 7.1 Hz, 2H), 5.22 and 5.23 (s, 1H), 5.99 (s, NH), 6.63 (d, J = 8.3 Hz, 2H), 7.14 (d, J = 8.3 Hz, 2H), 8.35 (s, NH) ppm.

*4-(4-N,N-Dimethylaniline)-5-(ethoxycarbonyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one* (Table 3, Entry 13)

Yield 94 % (recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 70:30, Rf = 0.35); M.p. 253–255 °C (250 °C)[42]; FT-IR: $\bar{\nu}_{max}$ (KBr) = 3235, 3200, 1719, 1699, 1647, 1461, 1618, 1563, 1525, 1458, 1365, 1312, 1254, 1088, 1217, 783 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d6) 1.22 (t, J = 7.1 Hz, 3H), 2.38 (s, 3H), 2.98 (s, 6H), 4.12 (q, J = 7.1 Hz, 1H), 4.14 (q, J = 7.1 Hz, 1H), 5.33 and 5.34 (s, 1H), 6.74 (d, J = 8.4 Hz, 2H), 7.20 (m, 2H and NH), 7.82 (s, NH) ppm.

*5-Ethoxycarbonyl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1*H*)-thione* (Table 3, Entry 14)

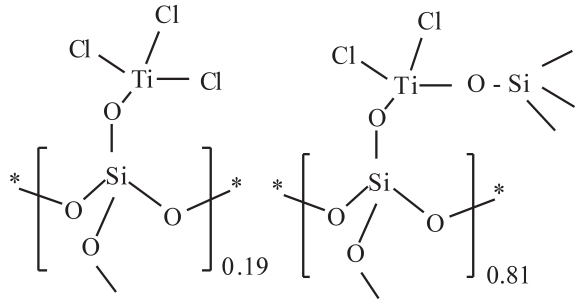
Yield 83 % (recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 70:30, Rf = 0.3); M.p. 191–193 °C (not found); FT-IR: $\bar{\nu}_{max}$ (KBr) = 3320, 3173,1670, 1573, 1510, 1462, 1395, 1370, 1327, 1030, 1174, 1116, 810 cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d6, ppm): 1.20 (t, J = 7.1 Hz, 3H), 2.34 (s, 3H), 2.37 (s, 3H), 4.10 (q, J = 7.1 Hz, 1H), 4.11 (q, J = 7.1 Hz, 1H), 5.36 and 5.37 (s, 1H), 7.13 (d, J = 8.1 Hz, 2H), 7.19 (d, J = 8.1 Hz, 2H), 8.01 (s, NH), 8.64 (s, NH) ppm.

*4-(4-Chlorophenyl)-5-methoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione* (Table 3, Entry 15)

Yield 77 % (Recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 70:30, Rf = 0.3); M.p. 206–209 °C (208 °C)[38]; FT-IR: $\bar{\nu}_{max}$ (KBr) = 3278, 3179, 1619, 1452, 1586, 1385, 1361, 1328, 1118, 828, 725 cm^{-1}.

*5-Acetyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-thione* (Table 3, Entry16)

Yield 82 % (Recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 70:30, Rf = 0.45); M.p. 161–162 °C (161–163 °C)[38]; FT-IR: $\bar{\nu}_{max}$ (KBr) = 3309, 3232, 1618, 1458, 1563, 1509, 1380, 1363, 1326, 1235, 1110, 1023, 828 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d6, ppm): 2.16 (s, 3H), 2.38 (s, 3H), 3.82 (s, 3H), 5.43 (s, 1H), 6.90 (d, J = 8.5 Hz, 2H), 7.18 (s, NH), 7.23 (d, J = 8.5 Hz, 2H), 7.63 (s, NH) ppm.



Scheme 1
Suggested structure for nano-$TiCl_4.SiO_2$.

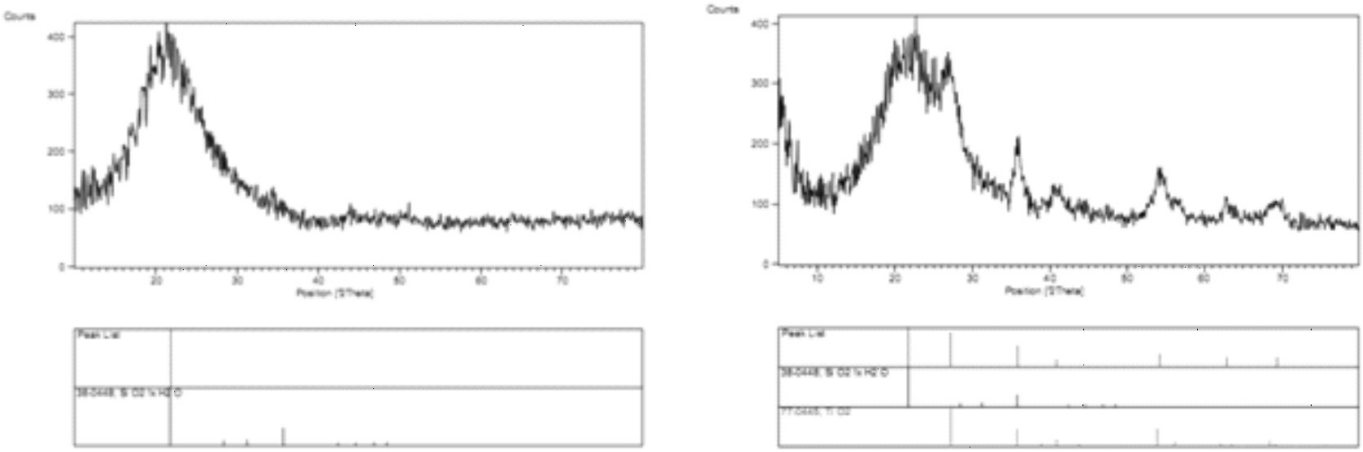


Figure 1 X-ray diffraction (XRD) pattern of (**a**) nano-SiO_2 and (**b**) nano-$TiCl_4.SiO_2$.

*4,6-Diphenyl-5-ethoxycarbonyl-3,4-dihydropyrimidin-2(1*H*)-thione* (Table 3, Entry 17)

Yield 87 % (recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 70:30, Rf = 0.3); M.p. 184–185 °C (183–185 °C)[38]; FT-IR: $\bar{\nu}_{max}$ (KBr) = 3313, 3152, 1672, 1641, 1492, 1600, 1566, 1458, 1367, 1334, 1107, 1203, 1130, 692, 763 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d60.85 (t, J = 7.1 Hz, 3H), 3.88 (q, J = 7.1 Hz, 1H), 3.89 (q, J = 7.1 Hz, 1H), 5.57 and 5.58 (s, 1H), 7.36–7.50 (m,10H and NH), 7.83 (s, NH) ppm.

*5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-phenyl-3,4-dihydropyrimidin-2(1*H*)-thione* (Table 3, Entry 18)

Yield 90 % (recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 70:30, Rf = 0.45); M.p. 152–153 °C (151–152 °C)[38]; FT-IR: $\bar{\nu}_{max}$ (KBr) = 3304, 3251, 1672, 1612, 1511, 1452, 1375, 1373, 1339, 1253, 1096, 1172, 1133, 1050, 824 cm^{-1}.

3. Results and Discussion

Nano-$TiCl_4.SiO_2$[25,26] as an efficient and reusable acidic catalyst is synthesized *via* the reaction of nano-silica gel with $TiCl_4$ in chloroform at room temperature. Recently, our study on the structure of nano-$TiCl_4.SiO_2$ has led to more exactly configuration containing SiO_2-$TiCl_3$ (19 %) and SiO_2-$TiCl_2$-SiO_2 (81 %) as demonstrated in Scheme 1.

The X-ray diffraction (XRD) patterns of nano-SiO_2 and nano-$TiCl_4.SiO_2$ are shown in Fig. 1. According to the Scherrer equation,[27] the broadening of peaks implies a decrease in crystalline size. The XRD pattern of nano-SiO_2 exhibits a strong peak at a 2θ value of 21.8024 ° with FWHM equal to 0.1771. From the XRD data of nano-$TiCl_4.SiO_2$, the values of 2θ and FWHM are presented in Table 1. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) images of nano-$TiCl_4.SiO_2$ are shown in Fig. 2. The particle size in the TEM pattern was calculated to be 14–20 nm using the GetData Graph program.

Table 1 Nano-$TiCl_4.SiO_2$ reflexes in XRD diffractogram.

Entry	Pos. [°2Th.]	FWHM [°2Th.]
1	21.7587	0.3542
2	27.1424	1.6531
3	35.8287	0.4723
4	40.8394	1.1808
5	54.1881	1.1808
6	62.8214	0.7085
7	69.3466	2.3040

For an investigation of the efficiency of nano-$TiCl_4.SiO_2$ in preparation of racemic 5-ethoxycarbonyl-6-methyl-4-phenyl-3-4-dihydropyrimidin-2(1*H*)-one, we examined the reaction of benzaldehyde (2 mmol, 0.21 mL), ethyl acetoacetate (2 mmol, 0.26 mL), urea (2.5 mmol, 0.15 g) as model reaction (Scheme 2). The reaction under different conditions in the presence of $TiCl_4.SiO_2$ or nano-$TiCl_4.SiO_2$ revealed that the best conditions were 0.12 g of $TiCl_4.SiO_2$ or 0.05 g of nano-$TiCl_4.SiO_2$ under solvent-free conditions at 60 °C (Table 2, Entries 1 and 9). Once the scope of the reaction condition was established, the reusability of catalyst was examined. After performing the reaction, the catalyst was separated, washed with acetone, dried and re-used up to three times in the same reaction without losing its activity (Fig. 3). This reaction was effectively scaled up to more than 10 grams of product.

Next, the applicability of this procedure was explored using a wide range of aromatic aldehydes containing electron-donating or electron-withdrawing groups (Table 3, Scheme 3). The three-component reaction proceeded smoothly to give the corre-

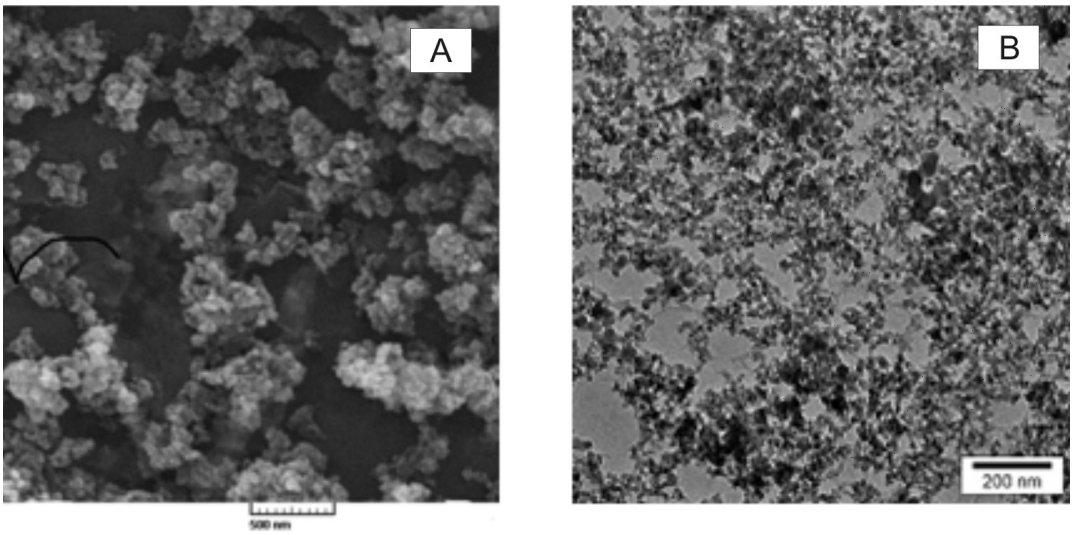
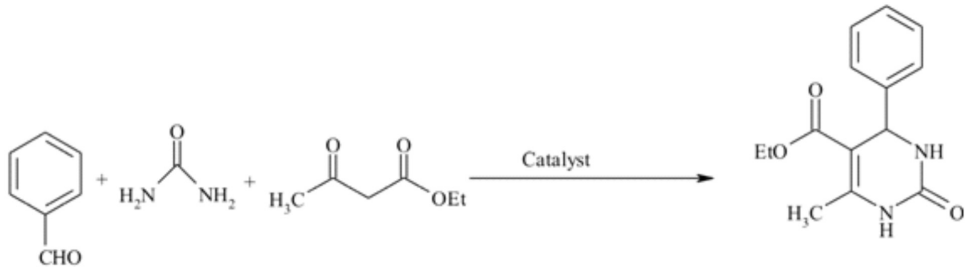


Figure 2 (**a**) SEM and (**b**) TEM photographs of nano-$TiCl_4.SiO_2$.



Scheme 2
Preparation of racemic 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one.

sponding racemic 3,4-dihydropyrimidin-2(1*H*)-ones/thiones in moderate to good yields. In all cases, aromatic aldehydes containing electron-withdrawing groups gave higher yields of products in shorter times than aromatic aldehydes containing electron-donating groups (Table 3, Entries 2 and 4).

Biginelli products have an α,β-unsaturated carbonyl group giving rise to *cis*- and *trans*-diastereomers due to sigma bond rotation around C1-C2 (Scheme 4). In the FT-IR spectra of

Table 2 Synthesis of racemic 5-ethoxycarbonyl-6-methyl-4-phenyl-3, 4-dihydropyrimidin-2(1*H*)-one under various conditions.[a]

Entry	Catalyst/g	Solvent	Conditions	Time/min	Yield/% Ref.
1	$TiCl_4.SiO_2$ (0.12)	Solvent free	60 °C	18	94
2	$TiCl_4.SiO_2$ (0.12)	Acetic acid	Reflux	110	83
3	$TiCl_4.SiO_2$ (0.12)	Ethanol		60	91
4	$TiCl_4.SiO_2$ (0.12)		Reflux	100	82
5	$TiCl_4.SiO_2$ (0.12)	Solvent free	MM[b]	135	52
6	$TiCl_4.SiO_2$ (0.12)	EtOAc	Sonication[c]	60	64
7	$TiCl_4.SiO_2$ (0.12)	Solvent free	MW[d]	30	70
8	Nano-50%$TiCl_4.SiO_2$ (0.07)	Solvent-free	60 °C	18	94
9	Nano-50%$TiCl_4.SiO_2$ (0.05)	Solvent-free	60 °C	18	93
10	Nano-50%$TiCl_4.SiO_2$ (0.03)	Solvent-free	60 °C	18	88
11	Nano-$TiCl_4.SiO_2$ (0.05), 2nd run	Solvent-free	60 °C	18	74
12	Nano-$TiCl_4.SiO_2$ (0.05), 3rd run	Solvent-free	60 °C	18	65
13	$ZrCl_4$ (10 mol%)	Ethanol	Reflux	240	88[13]
14	Trichloroisocyanuric acid (TCCA)	Ethanol	Reflux	720	94[22]
15	($TiCl_4$–$MgCl_2$/$MgCl_2$·$4CH_3OH$)	Solvent-free	100 °C	180	91[28]
16	H_3PO_3 (10 mol%) and $(PPh_3)_2PdCl_2$ (2.0 mol%)	pyrrolidine	80–120 °C	360	86[29]
17	Chloroacetic acid (10 mol%)	Solvent-free	90 °C	180	86[30]
18	$H_3PMo_{12}O_{40}$ (2 mol%)	Acetic acid	Reflux	240	75[31]
19	$Fe(CF_3CO_2)_3$ (5 mol%)	Solvent-free	70 °C	20	95[32]
20	$NaHSO_4.SiO_2$ (10 mol%)	Acetonitril	Reflux	120	88[33]
21	$Yb(NO_3)_3.6H_2O$ (5 mol%)	Solvent-free	70 °C	45	80[34]

[a] The amounts of starting material: benzaldehyde (2 mmol), ethyl acetoacetate (2 mmol), urea (2.5 mmol).
[b] Using mixer mill (MM 400) in 25 Hz frequency.
[c] Using BANDELIN Sonopulse HD 3200 Ultrasonic apparatus with power equal to 20 KHz.
[d] Using microwave oven, Kenwood, 1300 W.

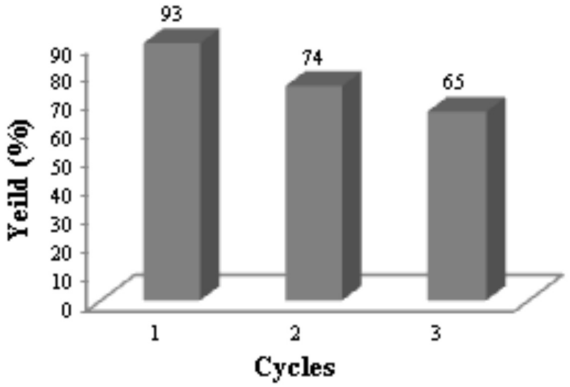
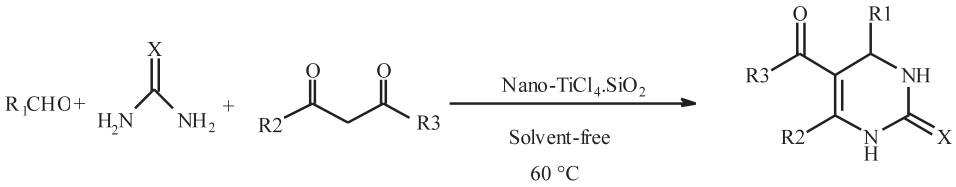


Figure 3 Reusability of nano-$TiCl_4.SiO_2$ catalyst.

3,4-dihydropyrimidin-2(1*H*)-ones containing an ester group, three carbonyl signals were observed. Two of them at ~1700 cm^{-1} are related to the α,β-unsaturated ester carbonyl group and the third signal nearly 1650 cm^{-1} is related to a urea type carbonyl band. In the FT-IR spectra of 3,4-dihydropyrimidin-2(1*H*)-thiones, only one stretching band is observed for the α,β-unsaturated ester carbonyl group nearly 1670 cm^{-1}. This indicates that the thiones are only in the *trans* form (Scheme 5). In the ^{1}H NMR spectra of some compounds such as 5-ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one, the CH_2 protons H(A) and H(B) are observed as two quartet peaks at 4.10 and 4.12 ppm integrating for two protons; H(C) is observed as two singlet peaks at 5.36 and 5.37 ppm integrating for one proton (Scheme 6).

4. Conclusion

In conclusion, nano-$TiCl_4.SiO_2$ is an efficient, cheap, non-corrosive, easily available, and reusable catalyst for the synthesis of racemic dihydropyrimidin-ones or thiones. The present procedure describes a useful improvement in the existing conditions for the Biginelli condensation. High to excellent yields, ease of work-up, mild reaction conditions, short reaction times, environmentally friendly procedures and the ability to tolerate a diversity of aldehyde substituents are attractive features of this new procedure.

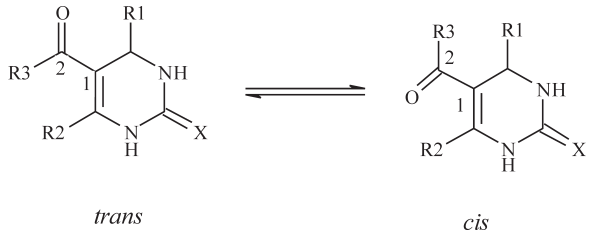


Scheme 3
Three-component reaction proceeded to give racemic 3,4-dihydropyrimidin-2(1*H*)-ones/thiones.

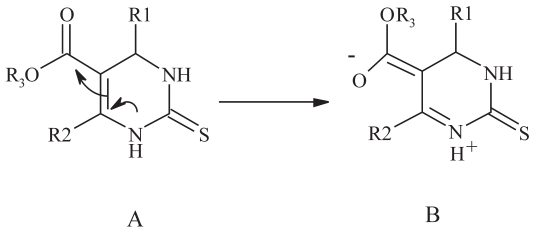
Table 3 Nano-$TiCl_4.SiO_2$ catalyzed synthesis of racemic 3,4-dihydropyrimidin-2(1*H*)-ones/thiones.

Entry	R^1	R^2	R^3	X	Time/min	Yield [a]	Mp/°C	
							Found	Reported[Ref.]
1	2-NO_2-C_6H_4	CH_3	OCH_2CH_3	O	20	90	218–219	221[31]
2	4-NO_2-C_6H_4	CH_3	OCH_2CH_3	O	18	95	210–211	211[31]
3	4-Cl-C_6H_4	CH_3	OCH_2CH_3	O	18	91	211–214	211–213[30]
4	4-MeO-C_6H_4	CH_3	OCH_2CH_3	O	22	80	201–204	203[31]
5	3-MeO-C_6H_4	CH_3	OCH_2CH_3	O	22	90	202–203	205–207[41]
6	4-Me-C_6H_4	CH_3	OCH_2CH_3	O	20	89	215–218	214[31]
7	Ph	CH_3	OCH_2CH_3	O	17	86	205–206	204[31]
8	C_6H_4-CH_2CH_2-	CH_3	OCH_2CH_3	O	26	89	155–157	152–153[40]
9	Ph	CH_3	CH_3	S	24	80	181–182	184[37]
10	C_6H_4-CH= CH-	CH_3	OCH_2CH_3	O	34	92	229–230	232–233[39]
11	2-Cl-5-NO_2-C_6H_3	Ph	OCH_2CH_3	S	36	78	236–238	239[38]
12	4-N,N-dimethylamino-Ph	CH_3	OCH_2CH_3	S	28	89	209–210	Not found
13	4-N,N-dimethylamino-Ph	CH_3	OCH_2CH_3	O	31	94	253–255	250[42]
14	4-Me-C_6H_4	CH_3	OCH_2CH_3	S	31	83	191–193	Not found
15	4-Cl-C_6H_4	CH_3	CH_3	S	27	77	206–209	208[38]
16	4-MeO-C_6H_4	CH_3	CH_3	S	40	82	161–162	161–163[38]
17	Ph	Ph	OCH_2CH_3	S	32	87	184–185	183–185[38]
18	4-MeO-C_6H_4	Ph	OCH_2CH_3	S	41	90	152–153	151–152[38]

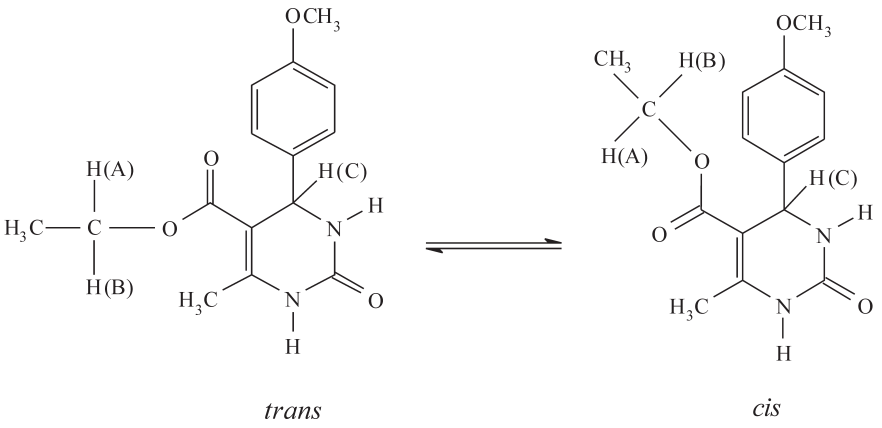
[a] The amounts of starting material: benzaldehyde (2 mmol), ethyl acetoacetate (2 mmol), urea (2.5 mmol), nano-$TiCl_4.SiO_2$ (0.05 g).



Scheme 4
Two *cis*- and *trans*-diastereomeric forms for 3,4-dihydropyrimidin-2(1*H*)-ones.



Scheme 5
Two resonance forms of 3,4-dihydropyrimidin-2(1*H*)-thiones.



trans *cis*

Scheme 6
Two *cis*- and *trans*-diastereomeric forms for 5-ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin- 2(1*H*)-one.

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