

Nano-TiCl₄.SiO₂: a Versatile and Efficient Catalyst for Synthesis of Dihydropyrimidones via Biginelli Condensation

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ABSTRACT

Nano-TiCl₄.SiO₂ 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-TiCl₄.SiO₂ as a solid Lewis acid has been synthesized by reaction of nano-SiO₂ and TiCl₄. 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-TiCl₄.SiO₂, 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-inflammatory⁴ 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 harmful.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 Ag₃PW₁₂O₄₀,⁹ LaCl₃.7H₂O¹⁰ La(OTf)₃,¹¹ Yb(OTf)₃,¹² ZrCl₄,¹³ BiCl₃,¹⁴ Mn(OAc)₃,¹⁵ LiClO₄,¹⁶ H₃BO₃,¹⁷ CeCl₃/InCl₃,¹⁸ Al(HSO₄)₃,¹⁹ KHSO₄,²⁰ ZnI₂,²¹ trichloroisocyanuric acid (TCCA),²² zeolite²³ and HBF₄.²⁴ 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-TiCl₄.SiO₂.

2. Experimental

2.1. General

The chemicals were obtained from Merck Company and used without any additional purification. The products were characterized by FT-IR (ATR), ¹H NMR, and a comparison of their phys-

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ical 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 ¹H NMR spectra. The X-ray diffraction (XRD) patterns of materials were recorded by employing a Philips Xpert MPD diffractometer equipped with a Cu K α anode ($\lambda = 1.54 \text{ \AA}$) in the 2 θ range from 10 to 80°. The SEM of nano particles was determined with a VEGA/TECAN scanning electron microscope and the TEM photograph was prepared on a Leo 912AB OMEGA microscope.

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

A mixture of aldehyde (2 mmol), ethyl acetoacetate/acetylacetone (2 mmol), urea/thiourea (2.5 mmol) and nano-TiCl₄.SiO₂ (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(1H)-one (Table 3, Entry 1)

Yield 90 % (recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 80:20, R_f = 0.4); M.p. 218–219 °C (221 °C)³¹; FT-IR: $\bar{\nu}_{\text{max}}$ (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(1H)-one (Table 3, Entry 2)

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

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

Yield 91 % (recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 80:20, $R_f = 0.4$); M.p. 211–214 °C (211–213 °C)³⁰; FT-IR: \bar{v}_{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(1H)-one (Table 3, Entry 4)

Yield 80 % (recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 80:20, $R_f = 0.5$); M.p. 201–204 °C (203 °C)³¹; FT-IR: \bar{v}_{max} (KBr) = 3237, 3116, 1722, 1702, 1647, 1511, 1588, 1583, 1541, 1458, 1367, 1251, 1086, 1218, 1031, 1277, 779 cm⁻¹, ¹H 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, NH), 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(1H)-one (Table 3, Entry 5)

Yield 90 % (recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 80:20, $R_f = 0.5$); M.p. 202–203 °C (205–207 °C)⁴¹; FT-IR: \bar{v}_{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(1H)-one (Table 3, Entry 6)

Yield 89 % (recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 80:20, $R_f = 0.3$); M.p. 215–218 °C (214 °C)³¹; FT-IR: \bar{v}_{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(1H)-one (Table 3, Entry 7)

Yield 86 % (recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 80:20, $R_f = 0.3$); M.p. 205–206 °C (204 °C)³¹; FT-IR: \bar{v}_{max} (KBr) = 3240, 3122, 1722, 1698, 1645, 1486, 1600, 1599, 1586, 1464, 1340, 1271, 1088, 1218, 699, 757 cm⁻¹, ¹H 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(1H)-one (Table 3, Entry 8)

Yield 89 % (Recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 80:20, $R_f = 0.27$); M.p. 155–157 °C (252–153 °C)⁴⁰; FT-IR: \bar{v}_{max} (KBr) = 3242, 3200, 1722, 1702, 1650, 1494, 1605, 1552, 1454, 1360, 1089, 1287, 1223, 695, 773 cm⁻¹, ¹H 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(1H)-thione (Table 3, Entry 9)

Yield 80 % (recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 70:30, $R_f = 0.3$); M.p. 181–182 °C (184 °C)³⁷; FT-IR: \bar{v}_{max} (KBr) = 3277, 3178, 1613, 1453, 1613, 1525, 1385, 1362, 1330, 1116, 694, 774 cm⁻¹. ¹H 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(1H)-one (Table 3, Entry 10)

Yield 92 % (recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 80:20, $R_f = 0.31$); M.p. 229–230 °C (232–233 °C)³⁹; FT-IR: \bar{v}_{max} (KBr) = 3239, 3113, 1721, 1698, 1650, 1486,

1602, 1583, 1463, 1366, 1286, 1089, 1223, 692, 755 cm⁻¹. ¹H 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(1H)-thione (Table 3, Entry 11)

Yield 78 % (recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 70:30, $R_f = 0.55$); M.p. 236–238 °C (239 °C)³⁸; FT-IR: \bar{v}_{max} (KBr) = 3257, 1666, 1494, 1602, 1551, 1525, 1440, 1398, 1375, 1344, 1344, 1063, 1199, 1142, 698 cm⁻¹. ¹H 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(1H)-thione (Table 3, Entry 12)

Yield 89 % (Recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 70:30, $R_f = 0.33$); M.p. 209–210 °C (not found); FT-IR: \bar{v}_{max} (KBr) = 3273, 3160, 1701, 1447, 1596, 1523, 1473, 1411, 1361, 1314, 1314, 1091, 1278, 1124, 814 cm⁻¹. ¹H 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(1H)-one (Table 3, Entry 13)

Yield 94 % (recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 70:30, $R_f = 0.35$); M.p. 253–255 °C (250 °C)⁴²; FT-IR: \bar{v}_{max} (KBr) = 3235, 3200, 1719, 1699, 1647, 1461, 1618, 1563, 1525, 1458, 1365, 1312, 1254, 1088, 1217, 783 cm⁻¹. ¹H 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(1H)-thione (Table 3, Entry 14)

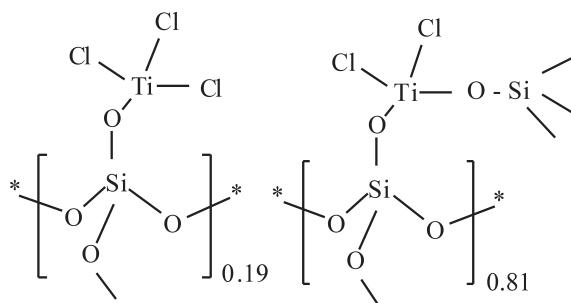
Yield 83 % (recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 70:30, $R_f = 0.3$); M.p. 191–193 °C (not found); FT-IR: \bar{v}_{max} (KBr) = 3320, 3173, 1670, 1573, 1510, 1462, 1395, 1370, 1327, 1030, 1174, 1116, 810 cm⁻¹. ¹H NMR (400 MHz, DMSO-d6, ppm): 1.20 (t, $J = 7.1$ Hz, 3H), 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(1H)-thione (Table 3, Entry 15)

Yield 77 % (Recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 70:30, $R_f = 0.3$); M.p. 206–209 °C (208 °C)³⁸; FT-IR: \bar{v}_{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(1H)-thione (Table 3, Entry 16)

Yield 82 % (Recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 70:30, $R_f = 0.45$); M.p. 161–162 °C (161–163 °C)³⁸; FT-IR: \bar{v}_{max} (KBr) = 3309, 3232, 1618, 1458, 1563, 1509, 1380, 1363, 1326, 1235, 1110, 1023, 828 cm⁻¹. ¹H 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-TiCl₄·SiO₂.

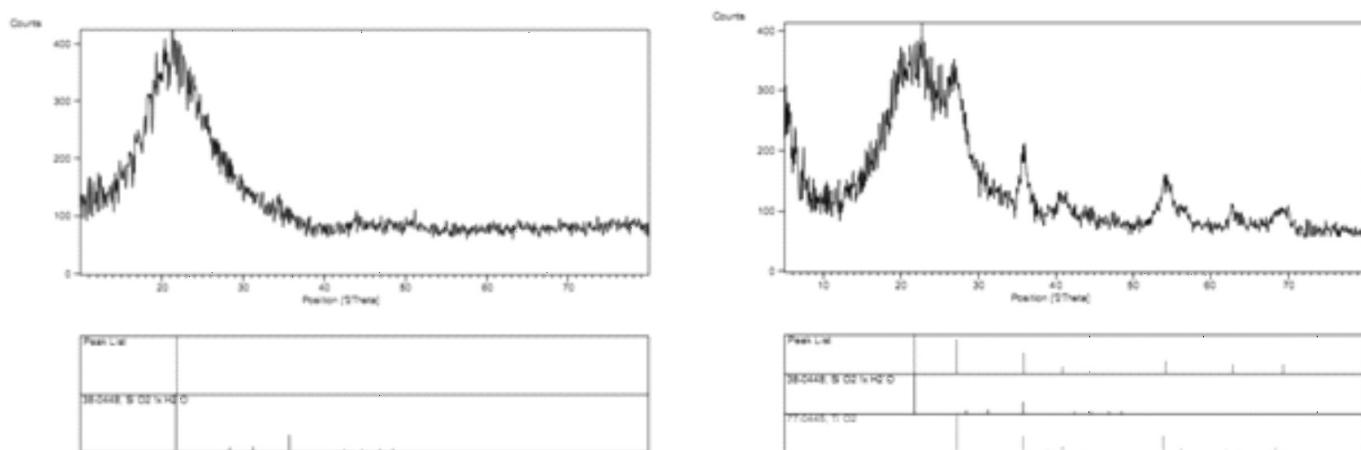


Figure 1 X-ray diffraction (XRD) pattern of (a) nano-SiO₂ and (b) nano-TiCl₄·SiO₂.

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

Yield 87 % (recrystallized from 85 % ethanol, TLC – chloroform:petroleum ether, 70:30, R_f = 0.3); M.p. 184–185 °C (183–185 °C)³⁸; FT-IR: \bar{v}_{max} (KBr) = 3313, 3152, 1672, 1641, 1492, 1600, 1566, 1458, 1367, 1334, 1107, 1203, 1130, 692, 763 cm⁻¹. ¹H NMR (500 MHz, DMSO-d6) δ 8.05–7.95 (m, 4H), 7.36–7.50 (m, 10H and NH), 7.83 (s, NH) ppm.

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

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

3. Results and Discussion

Nano-TiCl₄·SiO₂^{25,26} as an efficient and reusable acidic catalyst is synthesized via the reaction of nano-silica gel with TiCl₄ in chloroform at room temperature. Recently, our study on the structure of nano-TiCl₄·SiO₂ has led to more exactly configuration containing SiO₂–TiCl₃ (19 %) and SiO₂–TiCl₂–SiO₂ (81 %) as demonstrated in Scheme 1.

The X-ray diffraction (XRD) patterns of nano-SiO₂ and nano-TiCl₄·SiO₂ 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-SiO₂ exhibits a strong peak at a 2θ value of 21.8024 ° with FWHM equal to 0.1771. From the XRD data of nano-TiCl₄·SiO₂, the values of 2θ and FWHM are presented in Table 1. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) images of nano-TiCl₄·SiO₂ are shown in Fig. 2. The particle size in the

Table 1 Nano-TiCl₄·SiO₂ 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

TEM pattern was calculated to be 14–20 nm using the GetData Graph program.

For an investigation of the efficiency of nano-TiCl₄·SiO₂ in preparation of racemic 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-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 TiCl₄·SiO₂ or nano-TiCl₄·SiO₂ revealed that the best conditions were 0.12 g of TiCl₄·SiO₂ or 0.05 g of nano-TiCl₄·SiO₂ 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-

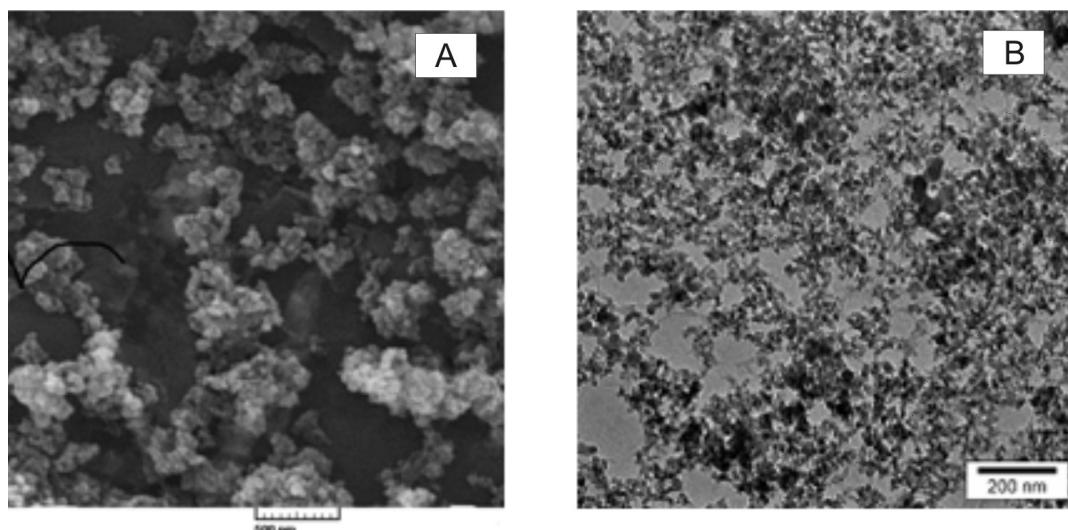
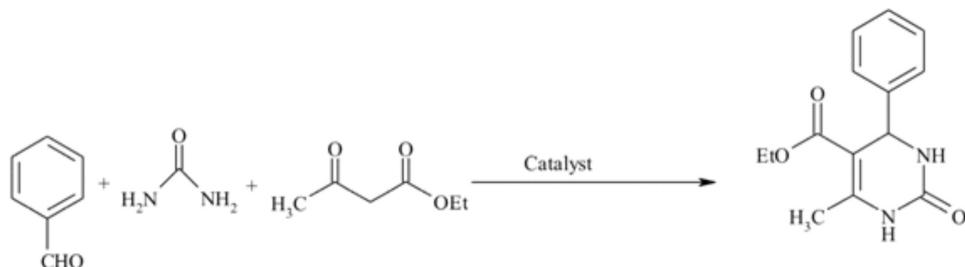


Figure 2 (a) SEM and (b) TEM photographs of nano-TiCl₄·SiO₂.



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

sponding racemic 3,4-dihydropyrimidin-2(1H)-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(1H)-one under various conditions.^a

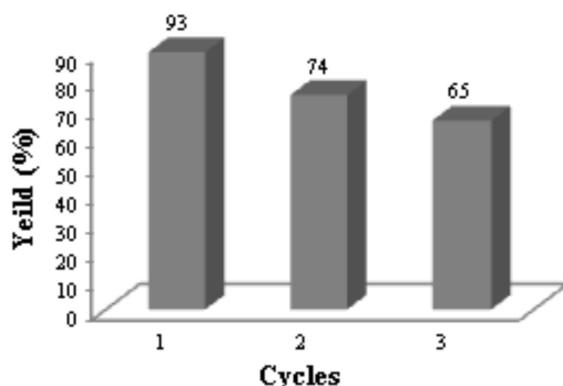
Entry	Catalyst/g	Solvent	Conditions	Time/min	Yield/% ^{Ref.}
1	TiCl ₄ ·SiO ₂ (0.12)	Solvent free	60 °C	18	94
2	TiCl ₄ ·SiO ₂ (0.12)	Acetic acid	Reflux	110	83
3	TiCl ₄ ·SiO ₂ (0.12)	Ethanol		60	91
4	TiCl ₄ ·SiO ₂ (0.12)		Reflux	100	82
5	TiCl ₄ ·SiO ₂ (0.12)	Solvent free	MM ^b	135	52
6	TiCl ₄ ·SiO ₂ (0.12)	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 ₃ OH)	Solvent-free	100 °C	180	91 ²⁸
16	H ₃ PO ₃ (10 mol%) and (PPh ₃) ₂ PdCl 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 ₃ PMo ₁₂ O ₄₀ (2 mol%)	Acetic acid	Reflux	240	75 ³¹
19	Fe(CF ₃ CO ₂) ₃ (5 mol%)	Solvent-free	70 °C	20	95 ³²
20	NaHSO ₄ ·SiO ₂ (10 mol%)	Acetonitrile	Reflux	120	88 ³³
21	Yb(NO ₃) ₃ ·6H ₂ O (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.

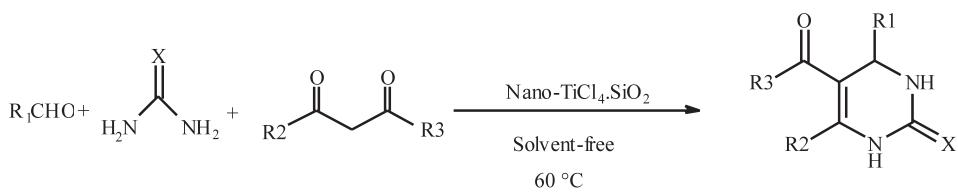
Figure 3 Reusability of nano-TiCl₄.SiO₂ catalyst.

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 ¹H NMR spectra of some compounds such as 5-ethoxy-carbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one, the CH₂ 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-TiCl₄.SiO₂ 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.

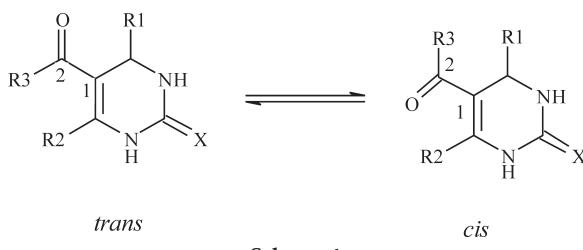


Scheme 3
Three-component reaction proceeded to give racemic 3,4-dihydropyrimidin-2(1*H*)-ones/thiones.

Table 3 Nano-TiCl₄.SiO₂ catalyzed synthesis of racemic 3,4-dihydropyrimidin-2(1*H*)-ones/thiones.

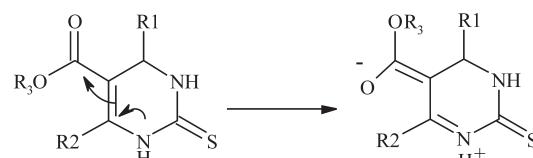
Entry	R ¹	R ²	R ³	X	Time/min	Yield ^a	Mp/°C	
							Found	Reported ^{Ref.}
1	2-NO ₂ -C ₆ H ₄	CH ₃	OCH ₂ CH ₃	O	20	90	218–219	221 ³¹
2	4-NO ₂ -C ₆ H ₄	CH ₃	OCH ₂ CH ₃	O	18	95	210–211	211 ³¹
3	4-Cl-C ₆ H ₄	CH ₃	OCH ₂ CH ₃	O	18	91	211–214	211–213 ³⁰
4	4-MeO-C ₆ H ₄	CH ₃	OCH ₂ CH ₃	O	22	80	201–204	203 ³¹
5	3-MeO-C ₆ H ₄	CH ₃	OCH ₂ CH ₃	O	22	90	202–203	205–207 ⁴¹
6	4-Me-C ₆ H ₄	CH ₃	OCH ₂ CH ₃	O	20	89	215–218	214 ³¹
7	Ph	CH ₃	OCH ₂ CH ₃	O	17	86	205–206	204 ³¹
8	C ₆ H ₄ -CH ₂ CH ₂ -	CH ₃	OCH ₂ CH ₃	O	26	89	155–157	152–153 ⁴⁰
9	Ph	CH ₃	CH ₃	S	24	80	181–182	184 ³⁷
10	C ₆ H ₄ -CH=CH-	CH ₃	OCH ₂ CH ₃	O	34	92	229–230	232–233 ³⁹
11	2-Cl-5-NO ₂ -C ₆ H ₃	Ph	OCH ₂ CH ₃	S	36	78	236–238	239 ³⁸
12	4-N,N-dimethylamino-Ph	CH ₃	OCH ₂ CH ₃	S	28	89	209–210	Not found
13	4-N,N-dimethylamino-Ph	CH ₃	OCH ₂ CH ₃	O	31	94	253–255	250 ⁴²
14	4-Me-C ₆ H ₄	CH ₃	OCH ₂ CH ₃	S	31	83	191–193	Not found
15	4-Cl-C ₆ H ₄	CH ₃	CH ₃	S	27	77	206–209	208 ³⁸
16	4-MeO-C ₆ H ₄	CH ₃	CH ₃	S	40	82	161–162	161–163 ³⁸
17	Ph	Ph	OCH ₂ CH ₃	S	32	87	184–185	183–185 ³⁸
18	4-MeO-C ₆ H ₄	Ph	OCH ₂ CH ₃	S	41	90	152–153	151–152 ³⁸

^aThe amounts of starting material: benzaldehyde (2 mmol), ethyl acetoacetate (2 mmol), urea (2.5 mmol), nano-TiCl₄.SiO₂ (0.05 g).



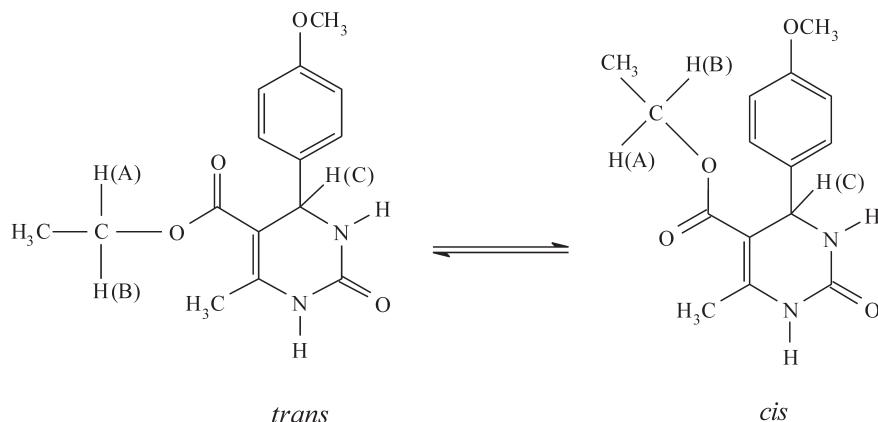
Scheme 4

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.



Scheme 6

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

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