TiCl$_2$/Nano-γ-Al$_2$O$_3$ as a Novel Lewis Acid Catalyst for Promotion of One-pot Synthesis of 1,4-dihydropyridines

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ABSTRACT

Synthesis of organic compounds using nano-catalysts is more and more attention due to the numerous advantages such as cost-effectiveness, high catalytic activity, ease of product separation, recovery of the catalyst, repeated recycling potential and good stability. In this work, TiCl$_2$/nano-γ-Al$_2$O$_3$ as a novel type of green heterogeneous solid acid was prepared by the immobilization of TiCl$_2$ on the surface of nano-γ-Al$_2$O$_3$ and characterized by Fourier transform-infrared spectroscopy (FT-IR), X-ray diffraction (XRD), field emission-scanning electron microscope (FE-SEM), energy dispersive X-ray (EDX), X-ray fluorescence spectroscopy (XRF), Brunauer–Emmett–Teller (BET) and thermal gravimetric analysis (TGA). One-pot multicomponent reactions (MCRs) have been extensively studied for their simple procedures, high selectivity and superior atom economy. The activity of TiCl$_2$/nano-γ-Al$_2$O$_3$ was probed via the synthesis of 1,4-dihydropyridine derivatives of three components coupling reaction of aldehyde, 1,3-dicabonyl compound and ammonium acetate under solvent free condition with excellent yields in short time. The obtained 1,4-dihydropyridine derivatives were characterized by FT-IR and $^1$H NMR spectra.

INTRODUCTION

In recent years, one-pot multicomponent reactions (MCRs) have been extensively studied for their simple procedures, high selectivity, and superior atom economy. Contrary to the classical methods to synthesize complex molecules by sequential procedure, MCRs which consist of two or more synthetic steps, are carried out without the separation of any intermediates, so as to reduce time and to save both energy and raw materials [1-4]. One of these synthetic methods is the Hantzsch reaction [5] that is the known synthesis of 1,4-dihydropyridines (1,4-DHPs) and their derivatives [6-8]. These compounds are an important class of compounds in the field of drugs and pharmaceuticals [9,10] such as calcium channel blockers [11,12], antitumor [13], anti-inflammatory [14], antitubercular [15], analgesic [16] and antithrombotic activities [17,18] and medicinally important drugs such as amlodipine, nifedipin, isradipine [19], nimodipin, felodipine and nisoldipine [20].

Catalysts that enhance reactions rates and product yield, with good selectivity and stability are of great technological importance. many catalysts consist of highly dispersed metal nanoparticles supported on porous silica, alumina, zeolites, mesoporous materials and other oxides and also in many cases non-supported metal nano-clusters. Nano-catalysts mimic homogeneous (high surface area, easily accessible) as well as heterogeneous (stable, easy to handle, easy to isolate) catalyst
systems. Today, synthesis of organic compounds using nano-catalysts is more and more attention due to the numerous advantages such as cost-effectiveness, high catalytic activity, ease of product separation, recovery of the catalyst, repeated recycling potential and good stability [21]. In this regard, our purpose in this research was developing the organic synthesis via solid acid nano-catalyst. TiCl2/nano-γ-Al2O3 as a novel Lewis acid catalyst for promotion of one-pot synthesis of 1,4-dihydropyridines.

MATERIALS AND METHODS

General
All compounds were purchased from Merck and Fluka chemical company and used without any additional purification. FT-IR spectra were run on a Bruker, Eqinox 55 spectrometer. A Bruker (DRX-400 Avance) NMR was used to record the 1H-NMR spectra. Melting points were determined by a Buchi melting point B-540 B.V.CHI apparatus and were uncorrected. X-ray diffraction pattern using Philips Xpert MP diffractometer was achieved. Field Emission Scanning Electron Microscopy (FE-SEM) was obtained on a Mira Tescan. Energy-Dispersive X-ray Spectroscopy (EDS) of TiCl2/nano-γ-Al2O3 was measured by EDS instrument, Phenom pro X. Brunauer–Emmett–Teller (BET) surface area analysis of catalyst was done with Micromeritics, Tristar II 3020 analyzer. XRF analysis was done with Bruker, 54 Explorer instrument. The thermal gravimetric analysis (TGA) was done with “STA 504” instrument. The products were characterized by FT-IR, 1H-NMR, and a comparison of their physical properties with those reported in the literature.

Preparation of nano-γ-Al2O3

In a beaker containing Al2(SO4)3.18 H2O (66 g), we have added drop-wise with vigorous stirring, an aqueous solution of NaOH (1M, 600 ml) to dissolved of aluminium sulfate and then precipitated Al(OH)3 as a white solid. The solid was filtered and washed with distilled water to remove the sulfate ions and dried. In a beaker containing Al(OH)3 (20 g), aqueous solution of NaOH (1M, 100 ml) was added to dissolved all of Al(OH)3 and converted it to soluble NaAl(OH)4. Then polyethylene glycole 4000 (0.3 % v/v) was added to resulted solution and converted it to Al2O3 by adding drop-wise aqueous solution of HCl (0.1 M) with vigorous mixing to reach pH=8. The obtained solid was isolated by centrifuge, washed with distilled water and then calcinated in 800 °C for 3 hours.

General procedure for the preparation of TiCl2/nano-γ-Al2O3

To a mixture of nano-γ-Al2O3 (1g) and CH2Cl2 (10 ml), TiCl4 (0.5 ml) was added drop wise. The resulting suspension was stirred for 1 hour at room temperature, filtered, washed with chloroform, and dried at room temperature.

General procedure for the synthesis of 1,4-dihydropyridine derivatives

A mixture of an aryl aldehyde (1 mmol), 1,3-dicarbonyl compound (2 mmol), ammonium acetate (1.5 mmol) and TiCl2/nano-γ-Al2O3 (0.05 g) was in the solvent free conditions stirred at 90 °C for the stipulated time mentioned in Table 3. The progress of the reaction was monitored by TLC. After completion of the reaction, 2 mmol of ethanol was added and the heterogeneous catalyst was filtered. After to the filtrate solution, add water to product obtained sediment.

Table 1. XRF analysis of TiCl2/nano-γ-Al2O3

<table>
<thead>
<tr>
<th>Sample</th>
<th>TiO2 (%)</th>
<th>NaCl (%)</th>
<th>Al2O3 (%)</th>
<th>Catalyst (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCPS</td>
<td>2318.4</td>
<td>516.5</td>
<td>498.2</td>
<td>646.7</td>
</tr>
<tr>
<td>Amount of element</td>
<td>60</td>
<td>60</td>
<td>53</td>
<td>16.8</td>
</tr>
</tbody>
</table>

Table 2. XRD analysis of TiCl2/nano-γ-Al2O3

<table>
<thead>
<tr>
<th>NO.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pos. [2θ]</td>
<td>31.900</td>
<td>37.676</td>
<td>45.666</td>
<td>67.253</td>
<td>75.537</td>
</tr>
<tr>
<td>FWHM [2θ]</td>
<td>0.236</td>
<td>1.574</td>
<td>0.393</td>
<td>0.472</td>
<td>1.152</td>
</tr>
</tbody>
</table>
Spectral data for selected compounds

Ethyl-2,7,7-trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (Entry 1, Table 4): Yellowish solid. M.p. 205-207 °C. IR (KBr)/ῡ (cm⁻¹): 3283, 1697, 1609, 1483, 1211. ¹H NMR (CDCl₃, 400 MHz)/δ ppm: 7.30 (d, J = 7.5 Hz, 2 H, Ar-H), 7.19 (t, J = 7.5 Hz, 2 H, Ar-H), 7.09 (t, J = 7 Hz, 1 H, Ar-H), 6.44 (s, 1 H, NH), 5.05 (s, 1 H, CH), 4.06 (q, J = 7.2 Hz, 2 H, OCH₂), 2.35 (s, 3 H, CH₃), 2.13–2.30 (m, 4 H, 2 CH₂), 1.18 (t, J = 7 Hz, 3 H, CH₂CH₂), 0.93 (s, 3 H, CH₃).

Ethyl-4-(4-chlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (Entry 2, Table 4): Yellow solid. M.p. 233-235 °C. IR (KBr)/ῡ (cm⁻¹): 3281, 1704, 1605, 1489, 1218, 1091. ¹H NMR (CDCl₃, 400 MHz)/δ ppm: 7.26 (d, J = 6.9 Hz, 2 H, Ar-H), 7.16 (d, J = 6.9 Hz, 2 H, Ar-H), 6.00 (s, 1 H, NH), 5.02 (s, 1 H, CH), 4.06 (q, J = 6.8 Hz, 2 H, OCH₂), 2.38 (s, 3 H, CH₃), 2.13–2.31 (m, 4 H, 2 CH₂), 1.19 (t, J = 6.8 Hz, 3 H, CH₂CH₂), 1.08 (s, 3 H, CH₃), 0.93 (s, 3 H, CH₃).

Ethyl-4-(4-nitrophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (Entry 3, Table 4): Yellow solid. M.p. 220-222 °C. IR (KBr)/ῡ (cm⁻¹): 3277, 1702, 1607, 1518, 1492, 1345, 1216. ¹H NMR (CDCl₃, 400 MHz)/δ ppm: 8.08...
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Table 4. Synthesis of 1,4-dihydropyridines in the presence of TiCl$_2$/nano-γ-Al$_2$O$_3$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>1,3-Dicarbonyl compounds</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)$^a$</th>
<th>mp.°C (Lit.)</th>
<th>Ref.</th>
</tr>
</thead>
</table>
| 1     | ![Image](image1.png) | 1 mmol A  
1 mmol B | ![Image](image2.png) | 1:30     | 90          | 205-207 (202-204) | 24   |
| 2     | ![Image](image3.png) | 1 mmol A,  
1 mmol B | ![Image](image4.png) | 3        | 80          | 233-235 (234-235) | 25   |
| 3     | ![Image](image5.png) | 1 mmol A  
1 mmol B | ![Image](image6.png) | 3        | 95          | 220-222 (244-246) | 26   |
| 4     | ![Image](image7.png) | 1 mmol A  
1 mmol B | ![Image](image8.png) | 5        | 65          | 250-252 (252-253) | 26   |
| 5     | ![Image](image9.png) | 1 mmol A  
1 mmol B | ![Image](image10.png) | 3        | 60          | 243-245       | -    |
| 6     | ![Image](image11.png) | 1 mmol A  
1 mmol B | ![Image](image12.png) | 2        | 70          | 210-212 (242-244) | 27   |
| 7     | ![Image](image13.png) | 1 mmol A  
1 mmol B | ![Image](image14.png) | 3        | 65          | 216-218       | -    |
| 8     | ![Image](image15.png) | 1 mmol A  
1 mmol B | ![Image](image16.png) | 4        | 50          | 210-212 (208-209) | 26   |
Continued Table 4. Synthesis of 1,4-dihydropyridines in the presence of TiCl$_2$/nano-γ-Al$_2$O$_3$.

<table>
<thead>
<tr>
<th>Entry</th>
<th>1 mmol A</th>
<th>1 mmol B</th>
<th>T (°C)</th>
<th>m.p. (°C)</th>
<th>IR (KBr) (cm$^{-1}$)</th>
<th>1H NMR (CDCl$_3$, 400 MHz)/δ ppm:</th>
<th>13C NMR (CDCl$_3$, 100 MHz)/δ ppm:</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>1 mmol A</td>
<td>1 mmol B</td>
<td>4</td>
<td>80</td>
<td>234-236</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1 mmol A</td>
<td>1 mmol B</td>
<td>6</td>
<td>90</td>
<td>176-177 (161-163)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>1 mmol A</td>
<td>1 mmol B</td>
<td>8</td>
<td>85</td>
<td>202-204</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>1 mmol A</td>
<td>1 mmol B</td>
<td>14</td>
<td>85</td>
<td>222-225 (229-231)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>1 mmol A</td>
<td>1 mmol B</td>
<td>7</td>
<td>90</td>
<td>194-196</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>1 mmol A</td>
<td>1 mmol B</td>
<td>4</td>
<td>62</td>
<td>218-220</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>2 mmol A</td>
<td></td>
<td>8</td>
<td>80</td>
<td>150-152 (152-154)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>2 mmol B</td>
<td></td>
<td>4</td>
<td>95</td>
<td>240-242</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>2 mmol A</td>
<td></td>
<td>10</td>
<td>65</td>
<td>150-152 (160-162)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(d, $J$ = 7.9 Hz, 2 H, Ar-H), 7.48 (d, $J$ = 7.9 Hz, 2 H, Ar-H), 5.91 (s, 1 H, NH), 5.15 (s, 1 H, CH), 4.05 (q, $J$ = 7.1 Hz, 2 H, OCH$_2$), 2.42 (s, 3 H, CH$_3$), 2.10-2.36 (m, 4 H, 2 CH$_2$), 1.17 (t, $J$ = 7.1 Hz, 3 H, CH$_2$CH$_3$), 1.09 (s, 3 H, CH$_3$), 0.91 (s, 3 H, CH$_3$). 13C NMR (CDCl$_3$, 100 MHz)/δ ppm: 195.84, 167.03, 154.72, 150.16, 146.11, 145.10, 128.97, 123.28, 110.55, 104.59, 58.22, 50.64, 40.60, 37.30, 32.62, 29.37, 26.98, 19.16, 14.21. Diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (Entry 15, Table 4): Yellow solid. M.p. 150-152 °C. IR (KBr)/δ (cm$^{-1}$): 3339, 1686, 1488, 1208. 1H NMR (CDCl$_3$, 400 MHz)/δ ppm: 7.28 (d, $J$ = 7 Hz, 2 H, Ar-H), 7.21 (t,
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Continued Table 4. Synthesis of 1,4-dihydropyridines in the presence of TiCl²/nano-γ-Al₂O₃

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield (%)</th>
<th>M.p. (°C)</th>
<th>IR (KBr)/υ (cm⁻¹)</th>
<th>1H NMR (CDCl₃, 400 MHz)/δ ppm:</th>
<th>13C NMR (CDCl₃, 100 MHz)/δ ppm:</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>(1 mmol), 1,3-dicarbonyl compounds (2 mmol), ammonium acetate (1.2 mmol) and catalyst (0.05 g) was used.</td>
<td>60</td>
<td>262-264 (270-272)</td>
<td>3274, 1642, 1480.</td>
<td>7.33 (d, J = 7.5 Hz, 2 H, Ar-H), 6.71 (d, J = 7.5 Hz, 2 H, Ar-H), 6.54 (s, 1 H, NH), 5.09 (t, J = 7.5 Hz, 2 H, Ar-H), 5.08 (s, 1 H, CH₃), 2.14–2.39 (m, 8 H, 4 CH₂), 1.08 (s, 6 H, 2 CH₃), 0.97 (s, 6 H, 2 CH₃).</td>
<td>196.37, 157.62, 149.90, 139.30, 128, 92, 113.27, 113.09, 54.97, 50.96, 40.36, 32.76, 29.61, 27.05.</td>
</tr>
<tr>
<td>19</td>
<td>(1 mmol)</td>
<td>75</td>
<td>144-146 (145-146)</td>
<td>3339, 1688, 1510.</td>
<td>7.30 (d, J = 7.9 Hz, 2 H, Ar-H), 6.75 (d, J = 7.9 Hz, 2 H, Ar-H), 5.54 (s, 1 H, NH), 4.93 (s, 1 H, CH), 4.10 (q, J = 7.4 Hz, 4 H, 2 OCH₂), 3.76 (s, 3 H, OCH₃), 2.33 (s, 6 H, 2 CH₃), 1.23 (t, J = 7.4 Hz, 2 H, 2 CH₂).</td>
<td>196.37, 157.62, 149.90, 139.30, 128, 92, 113.27, 113.09, 54.97, 50.96, 40.36, 32.76, 29.61, 27.05.</td>
</tr>
<tr>
<td>20</td>
<td>(2 mmol) B</td>
<td>85</td>
<td>290-292 (298-300)</td>
<td>3339, 1688, 1510.</td>
<td>7.20 (d, J = 7.9 Hz, 2 H, Ar-H), 6.75 (d, J = 7.9 Hz, 2 H, Ar-H), 5.54 (s, 1 H, NH), 4.93 (s, 1 H, CH), 4.10 (q, J = 7.4 Hz, 4 H, 2 OCH₂), 3.76 (s, 3 H, OCH₃), 2.33 (s, 6 H, 2 CH₃), 1.23 (t, J = 7.4 Hz, 2 H, 2 CH₂).</td>
<td>196.37, 157.62, 149.90, 139.30, 128, 92, 113.27, 113.09, 54.97, 50.96, 40.36, 32.76, 29.61, 27.05.</td>
</tr>
<tr>
<td>21</td>
<td>(2 mmol A)</td>
<td>77</td>
<td>120-123 (128-130)</td>
<td>3339, 1688, 1510.</td>
<td>7.20 (d, J = 7.9 Hz, 2 H, Ar-H), 6.75 (d, J = 7.9 Hz, 2 H, Ar-H), 5.54 (s, 1 H, NH), 4.93 (s, 1 H, CH), 4.10 (q, J = 7.4 Hz, 4 H, 2 OCH₂), 3.76 (s, 3 H, OCH₃), 2.33 (s, 6 H, 2 CH₃), 1.23 (t, J = 7.4 Hz, 2 H, 2 CH₂).</td>
<td>196.37, 157.62, 149.90, 139.30, 128, 92, 113.27, 113.09, 54.97, 50.96, 40.36, 32.76, 29.61, 27.05.</td>
</tr>
<tr>
<td>22</td>
<td>(2 mmol B)</td>
<td>85</td>
<td>210-212 (289-291)</td>
<td>3339, 1688, 1510.</td>
<td>7.20 (d, J = 7.9 Hz, 2 H, Ar-H), 6.75 (d, J = 7.9 Hz, 2 H, Ar-H), 5.54 (s, 1 H, NH), 4.93 (s, 1 H, CH), 4.10 (q, J = 7.4 Hz, 4 H, 2 OCH₂), 3.76 (s, 3 H, OCH₃), 2.33 (s, 6 H, 2 CH₃), 1.23 (t, J = 7.4 Hz, 2 H, 2 CH₂).</td>
<td>196.37, 157.62, 149.90, 139.30, 128, 92, 113.27, 113.09, 54.97, 50.96, 40.36, 32.76, 29.61, 27.05.</td>
</tr>
</tbody>
</table>
RESULTS AND DISCUSSION

This research was performed in two steps. Firstly, TiCl2/nano-γ-Al2O3 as a novel Lewis acid catalyst were prepared and identified by FT-IR, XRD, BET, FE-SEM, EDX, and XRF techniques. In the second step, 1,4-dihydropyridine derivatives were synthesized by aryl aldehydes, 1,3-dicarbonyl compounds, and ammonium acetate under solvent free method and then characterized by their melting points using FT-IR, 1H NMR, 13C NMR, spectroscopy.

For identification of the structure of TiCl2/nano-γ-Al2O3, we have studied FT-IR (ATR) spectra of TiCl4 (aq), nano-γ-Al2O3 and TiCl2/nano-γ-Al2O3 (Fig. 2). In TiCl4 (aq) spectrum, a broad band at 3298 (H2O), a middle band at 1619 (Ti-Cl) and a strong band at 850 cm⁻¹ (Ti-O) were observed (Fig. 1a). In nano-γ-Al2O3 FT-IR spectrum, a very strong band at 600-1000 cm⁻¹ (Al-O) was observed (Fig. 1b). TiCl2/nano-γ-Al2O3, in addition to γ-Al2O3 signal, two additional bands at 1619 and 3298 show binding of TiCl2 to γ-Al2O3 (Fig. 1c).

The FE-SEM images of the TiCl2/nano-γ-Al2O3 and nano-γ-Al2O3 nanoparticles are displayed in Fig. 2. They exhibit irregular spherical shape for nano particles below 50 nm.

Energy-Dispersive X-ray Spectroscopy (EDS) of TiCl2/nano-γ-Al2O3 was measured by EDS instrument (Fig. 3) provided the presence of the expected elements in the structure of this catalyst and confirmed supporting of TiCl4 on nano-γ-Al2O3. The elemental compositions of TiCl2/nano-γ-Al2O3 were found to be 58.5, 29.9 and 6.5% for O, Al and...
To investigate the elemental component of \( \text{TiCl}_2/\text{nano-} \gamma \text{-Al}_2\text{O}_3 \), XRF analysis was performed. XRF analysis of catalyst was done by comparison of its Kilo Counts per Seconds (KCPS) with pure samples. In our catalyst, \( \text{TiCl}_2/\text{nano-} \gamma \text{-Al}_2\text{O}_3 \), the percentage of elements, Ti, Cl and Al, were determined via comparison with KCPS of pure \( \text{TiO}_2 \), \( \text{NaCl} \) and \( \text{Al}_2\text{O}_3 \) as can be seen in Table 1. 16.8 g of Ti and 23.8 g of Cl are equal to 0.35 mol and 0.67 mol, respectively, thus, the ratio of Ti:Cl is 1:2.

The X-ray diffraction (XRD) pattern of \( \text{TiCl}_2/\text{nano-} \gamma \text{-Al}_2\text{O}_3 \) is shown in (Fig. 5). According to XRD pattern of catalyst, the values of 2θ and FWHM are shown in Table 2. The signals at 2θ equal to 37, 45 and 67 are shown nano-\( \gamma \text{-Al}_2\text{O}_3 \) structure. According to XRD pattern, the two additional signals at 2θ equal to 32, 75 with FWHM equal to 0.236 and 1.152 respectively, are shown the presence of bonded Ti to nano-\( \gamma \text{-Al}_2\text{O}_3 \) (Fig. 4).

The specific surface area of catalyst was measured by Brunauer–Emmett–Teller (BET) theory. Single point surface area at \( \text{P/P}_0 = \)
Fig. 4. XRD patterns of TiCl$_2$/nano-$\gamma$-Al$_2$O$_3$

Fig. 5. Nitrogen adsorption isotherm at 77 K on TiCl$_2$/nano-$\gamma$-Al$_2$O$_3$

Fig. 6. Thermal gravimetric analysis (TG-DTG) pattern of TiCl$_2$/nano-$\gamma$-Al$_2$O$_3$
0.184317546 is 73.9645 m²/g and BET surface area is 75.5925 m²/g. The N₂ adsorption isotherm of catalyst is depicted in Fig. 5.

Thermal gravimetric analysis (TG-DTA) pattern of TiCl₂/nano-γ-Al₂O₃ was detected by heating from 50 °C to 400 °C and then cooling until 165 °C (Fig. 6).

The catalyst is stable until 392 °C and only 10.5 % of its weight was reduced due to the removal of catalyst moisture. The char yield of the catalyst in 392 °C is 89.5 %. According to the TG-DTA diagram of TiCl₂/nano-γ-Al₂O₃ and our study, it was revealed that this catalyst is suitable for the promotion of organic reactions until 400 °C.

Based on these results, we have also suggested the following structure for TiCl₂/nano-γ-Al₂O₃ (Fig. 7).

For evaluation of the catalytic activity of TiCl₂/nano-γ-Al₂O₃, initially, we have decided to explore the role of TiCl₂/nano-γ-Al₂O₃ for the synthesis of 1,4-dihydropyridines in a typical reaction to determine the optimum conditions. The reaction was performed under reflux conditions using various solvents such as ethanol, water, chloroform, n-hexane and dichloromethane (Table 3, entries 1–5), the microwave irradiation condition, that produced more than one product (Table 3, 6, 7), ultrasonic irradiation, its yield was negligible (Table 3, entry 8) and Solvent-free conditions, at different temperatures and different amounts of catalyst (Table 3, entries 9–16).

As shown in Table 3, the most yield of reaction was acquired in Solvent-free conditions at 90 °C in the presence of 0.05 g TiCl₂/nano-γ-Al₂O₃ after 90 minutes (Table 3, Entry 12).

Finally, a range of aryl aldehydes were subjected to react with 1,3-dicarbonyl compounds and ammonium acetate in the presence of 0.05 g of TiCl₂/nano-γ-Al₂O₃ to generate 1,4-DHPs. The results are summarized in Table 4. As listed in Table 4, aromatic aldehydes possessing different substituents such as OMe, OEt, NO₂, Cl, Br and NH₂ were converted to the corresponding 1,4-DHPs in good yields. Therefore TiCl₂/nano-γ-Al₂O₃ activates the carbonyl group of aldehyde as a Lewis acid in the synthesis of 1,4-DHPs.

Fig. 7. The proposed structure for TiCl₂/nano-γ-Al₂O₃

Fig. 8. Proposed mechanism for the synthesis of 1,4-dihydropyridines
CONCLUSIONS

In summary, we have developed a simple, efficient, and green protocol for synthesis of 1,4-dihydropyridines using TiCl\(_2\)/nano-\(\gamma\)-Al\(_2\)O\(_3\) as a novel heterogeneous solid acid catalyst under solvent-free conditions at 90°C temperature. The short reaction times, simple workup, good to excellent yields, mild reaction conditions, and use of nontoxic and noncorrosive catalyst are important features of this new method. In addition, recyclability of the catalyst caused that this methodology be a valid contribution to the existing processes in the field of Hantzsch reaction.

Acknowledgements

The proposed mechanism for the formation of 1,4-dihydropyridines in the presence of TiCl\(_2\)/
nano-\(\gamma\)-Al\(_2\)O\(_3\), which can act as Lewis acid catalyst (empty \(\pi\) orbital of Sn in TiCl\(_2\)/nano-\(\gamma\)-Al\(_2\)O\(_3\)) is depicted in Fig. 8.

The reusability of the catalysts is one of the most important benefits and makes them useful for commercial applications. Thus, after the completion of the reaction, the catalyst was separated. The recovered catalyst was washed with ethanol (20 mL) and dried at room temperature without further purification to use for the next run in current reaction under identical condition. As can be seen, the catalyst could be reused for third times without any appreciable loss of its activity (Fig. 9).

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

REFERENCES


