J Nanostruct 8(3): 276-287, Summer 2018

RESEARCH PAPER

# $TiCl_2$/Nano-γ-$Al_2O_3$ as a Novel Lewis Acid Catalyst for Promotion of One-pot Synthesis of 1,4-dihydropyridines

***Bi Bi Fatemeh Mirjalili[1]*, Abdolhamid Bamoniri[2], Leila Asadollah Salmanpoor[1]***

[1] *Department of Chemistry, College of Science, Yazd University, Yazd, Iran*

[2] *Department of Organic Chemistry, Faculty of Chemistry, University of Kashan, Kashan, Iran*

**ARTICLE INFO**

***Article History:***
*Received 25 November 2017*
*Accepted 3 May 2018*
*Published 01 July 2018*

***Keywords:***
*1,4-dihydropyridines*
*Heterogeneous Catalyst*
*Nano-γ-$Al_2O_3$*
*Solvent-Free Conditions*
*$TiCl_2$/Nano-γ-$Al_2O_3$*

**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-$Al_2O_3$, as a novel type of green heterogeneous solid acid was prepared by the immobilization of $TiCl_2$ on the surface of nano-γ-$Al_2O_3$ 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-$Al_2O_3$ 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.

**How to cite this article**
*NAMES N. $TiCl_2$/Nano-γ-$Al_2O_3$ as a Novel Lewis Acid Catalyst for Promotion of One-pot Synthesis of 1,4-dihydropyridines. J Nanostruct, 2018; 8(3): 276-287. DOI: 10.22052/JNS.2018.03.007*

## 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

* *Corresponding Author Email: fmirjalili@yazd.ac.ir*

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. $TiCl_2$/nano-γ-$Al_2O_3$ 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 $^1$H-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 $TiCl_2$/nano-γ-$Al_2O_3$ 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, S4 Explorer instrument. The thermal gravimetric analysis (TGA) was done with "STA 504" instrument. The products were characterized by FT-IR, $^1$H-NMR, and a comparison of their physical properties with those reported in the literature.

*Preparation of nano-γ-$Al_2O_3$*

In a beaker containing $Al_2(SO_4)_3$.18 $H_2O$ (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,100ml) was added to dissolved all of $Al(OH)_3$ and converted it to soluble $Na(Al(OH)_4)$. Then polyethylene glycole 4000 (0.3 % v/v) was added to resulted solution and converted it to $Al_2O_3$ 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 $TiCl_2$/nano-γ-$Al_2O_3$*

To a mixture of nano-γ-$Al_2O_3$ (1g) and $CH_2Cl_2$ (10 ml), $TiCl_4$ (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 $TiCl_2$/nano-γ-Al $_2O_3$ (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 (n-hexane: EtOAc, 7:3). The progress of the reacion was monitored by TLC. After completion of the reaction, 2 mmol of ethanol was add and the heterogeneous catalyst was filtered. After to the filtrate solution, add water to product obtained sediment.

Table 1. XRF analysis of $TiCl_2$/nano-γ-$Al_2O_3$

| Sample | $TiO_2$ | NaCl | $Al_2O_3$ | Catalyst | | |
|---|---|---|---|---|---|---|
| KCPS | 2318.4 ($TiO_2$) | 516.5 (Cl) | 498.2 ($Al_2O_3$) | 646.7 ($TiO_2$) | 204.6 (Cl) | 296.2 ($Al_2O_3$) |
| Amount of element (%) | 60 (Ti) | 60 (Cl) | 53 (Al) | 16.8 (Ti) | 23.8 (Cl) | 31.5 (Al) |

Table 2. XRD analysis of $TiCl_2$/nano-γ-$Al_2O_3$

| NO. | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Pos. [°2Th.] | 31.900 | 37.676 | 45.666 | 67.253 | 75.537 |
| FWHM [°2Th.] | 0.236 | 1.574 | 0.393 | 0.472 | 1.152 |

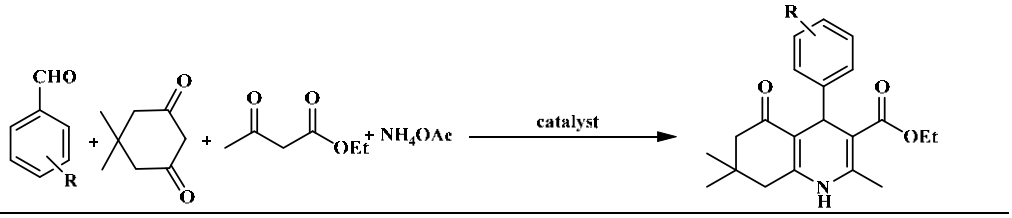
*Spectral data for selected compounds*

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)/ū ($cm^{-1}$): 3283, 1697, 1609, 1483 , 1211. $^1$H NMR ( $CDCl_3$, 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* = 7.2 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, $OCH_2$), 2.35 (s, 3 H, $CH_3$), 2.13–2.30 (m, 4 H, 2 $CH_2$), 1.18 (t, *J* =7.2 Hz, 3 H, $CH_3CH_2$), 1.07 (s, 3 H, $CH_3$), 0.93 (s, 3 H, $CH_3$).

Ethyl-4-(4-chlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3carboxylate (Entry 2, Table 4): Yellow solid. M.p. 233-235 °C. IR (KBr)/ū ($cm^{-1}$): 3281, 1704, 1605, 1489, 1218, 1091. $^1$H NMR ($CDCl_3$, 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, $OCH_2$), 2.38 (s, 3 H, $CH_3$), 2.13–2.31 (m, 4 H, 2 $CH_2$), 1.19 (t, *J*= 6.8 Hz, 3 H, $CH_3CH_2$), 1.08 (s, 3 H, $CH_3$), 0.93 (s, 3 H, $CH_3$).

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)/ū ($cm^{-1}$): 3277, 1702, 1607, 1518, 1492, 1345, 1216. $^1$H NMR ($CDCl_3$, 400 MHz)/δ ppm: 8.08

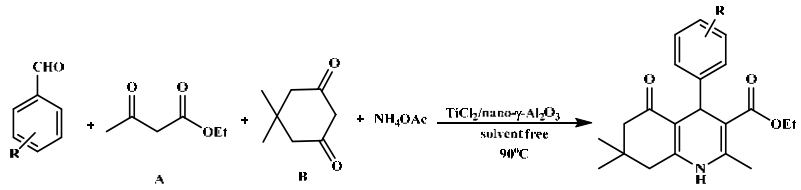
Table 3. The condensation reaction of 1,4-dihydropyridines with aromatic aldehydes, ethyl acetoacetate, dimedone and ammonium acetate under various conditions

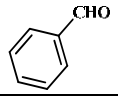
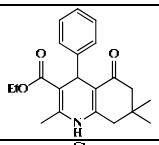
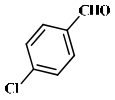
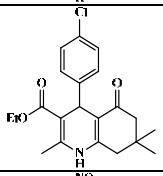
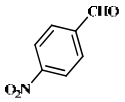
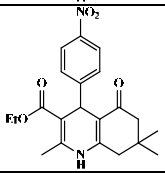
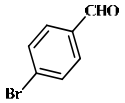
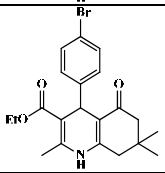
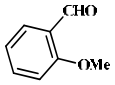
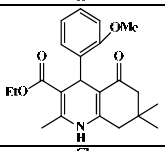
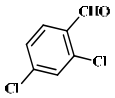
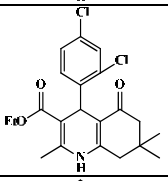
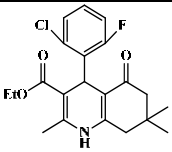
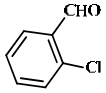
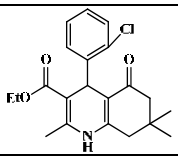



| Entry | Solvent | Temperature (°C) | Catalyst (g) | Time (min) | Yield (%)[a] | Ref. |
|---|---|---|---|---|---|---|
| 1 | Ethanol (2 ml) | Reflux | $TiCl_2$/nano-γ-$Al_2O_3$ (0.05) | 240 | 55 | - |
| 2 | Water (2 ml) | Reflux | $TiCl_2$/nano-γ-$Al_2O_3$ (0.05) | 240 | 40 | - |
| 3 | Chloroform (2 ml) | Reflux | $TiCl_2$/nano-γ-$Al_2O_3$ (0.05) | 240 | 35 | - |
| 4 | n- hexane (2 ml) | Reflux | $TiCl_2$/nano-γ-$Al_2O_3$ (0.05) | 240 | 70 | - |
| 5 | Dichloromethane (2 ml) | Reflux | $TiCl_2$/nano-γ-$Al_2O_3$ (0.05) | 240 | 50 | - |
| 6 | Water (2 ml) | MW | $TiCl_2$/nano-γ-$Al_2O_3$ (0.05) | 15 | - | - |
| 7 | Ethanol (2 ml) | MW | $TiCl_2$/nano-γ-$Al_2O_3$ (0.05) | 15 | - | - |
| 8 | Ethanol (2 ml) | U.S | $TiCl_2$/nano-γ-$Al_2O_3$ (0.05) | 60 | 60 | - |
| 9 | Neat | 25 | No catalyst | 240 | 20 | - |
| 10 | Neat | 90 | No catalyst | 240 | 40 | - |
| 11 | Neat | 90 | $TiCl_2$/nano-γ-$Al_2O_3$ (0.03) | 360 | 60 | - |
| 12 | Neat | 90 | $TiCl_2$/nano-γ-$Al_2O_3$ (0.05) | 90 | 90 | - |
| 13 | Neat | 90 | $TiCl_2$/nano-γ-$Al_2O_3$ (0.07) | 240 | 85 | - |
| 14 | Neat | r.t | $TiCl_2$/nano-γ-$Al_2O_3$ (0.05) | 90 | 20 | - |
| 15 | Neat | 50 | $TiCl_2$/nano-γ-$Al_2O_3$ (0.05) | 90 | 40 | - |
| 16 | Neat | 120 | $TiCl_2$/nano-γ-$Al_2O_3$ (0.05) | 90 | 90 | - |
| 17 | Neat | 80 | Magnetic $Fe_3O_4$ nanoparticles (7 mol %) | 5 | 94 | 23 |
| 18 | Ethanol | r.t | Cu/HCl | 180 | 98 | 24 |

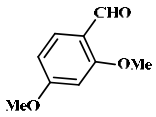
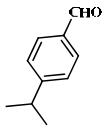
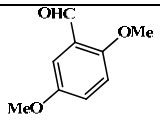
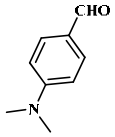
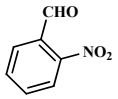
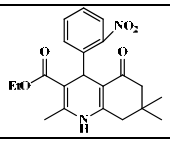
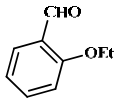
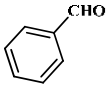
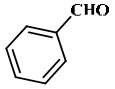
solated yield

Table 4. Synthesis of 1,4-dihydropyridines in the presence of $TiCl_2$/nano-γ-$Al_2O_3$




| Entry | Aldehyde | 1,3-Dicarbonyl compounds | Product | Time (h) | Yield (%)[b] | mp.°C (Lit.) | Ref. |
|---|---|---|---|---|---|---|---|
| 1 |  | 1 mmol A<br>1 mmol B |  | 1:30 | 90 | 205-207 (202-204) | 24 |
| 2 |  | 1 mmol A,<br>1 mmol B |  | 3 | 80 | 233-235 (234-235) | 25 |
| 3 |  | 1 mmol A<br>1 mmol B |  | 3 | 95 | 220-222<br>(244-246) | 26 |
| 4 |  | 1 mmol A<br>1 mmol B |  | 5 | 65 | 250-252 (252-253) | 26 |
| 5 |  | 1 mmol A<br>1 mmol B |  | 3 | 60 | 243-245 | - |
| 6 |  | 1 mmol A<br>1 mmol B |  | 2 | 70 | 210-212 (242-244) | 27 |
| 7 |  | 1 mmol A<br>1 mmol B |  | 3 | 65 | 216-218 | - |
| 8 |  | 1 mmol A<br>1 mmol B |  | 4 | 50 | 210-212 (208-209) | 26 |

Continued Table 4. Synthesis of 1,4-dihydropyridines in the presence of $TiCl_2$/nano-γ-$Al_2O_3$

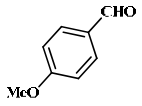
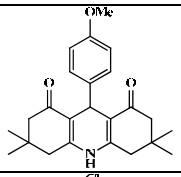
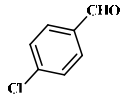
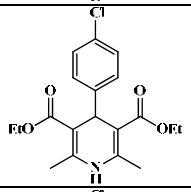
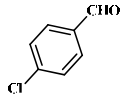
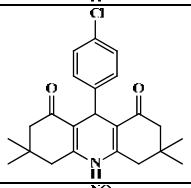
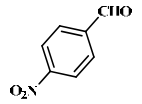
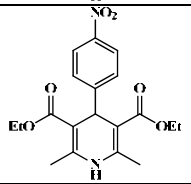
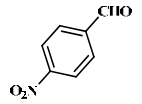
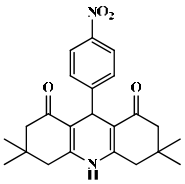
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **9** |  | 1 mmol A<br>1 mmol B | | 4 | 80 | 234-236 | - |
| **10** |  | 1 mmol A<br>1 mmol B | | 6 | 90 | 176-177 (161-163) | 28 |
| **11** |  | 1 mmol A<br>1 mmol B | | 8 | 85 | 202-204 | - |
| **12** |  | 1 mmol A<br>1 mmol B | | 14 | 85 | 222-225 (229-231) | 24 |
| **13** |  | 1 mmol A<br>1 mmol B |  | 7 | 90 | 194-196 | - |
| **14** |  | 1 mmol A<br>1 mmol B | | 4 | 62 | 218-220 | - |
| **15** |  | 2 mmol A | | 8 | 80 | 150-152 (152-154) | 29 |
| **16** |  | 2 mmol B | | 4 | 95 | 240-242 | - |
| **17** | | 2 mmol A | | 10 | 65 | 150-152 (160-162) | 30 |

(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, $CH_3CH_2$), 1.09 (s, 3 H, $CH_3$), 0.91 (s, 3 H, $CH_3$). $^{13}C$ 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-diethylcarboxylate (Entry 15, Table 4):

Yellow solid. M.p. 150-152 °C. IR (KBr)/ū (cm$^{-1}$): 3339, 1686, 1488, 1208. $^1H$ NMR ($CDCl_3$, 400 MH)/δ ppm: 7.28 (d, *J*= 7 Hz, 2 H. Ar-H), 7.21 (t,

Continued Table 4. Synthesis of 1,4-dihydropyridines in the presence of $TiCl_2$/nano-γ-$Al_2O_3$

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **18** |  | 2 mmol B |  | 8 | 60 | 262-264 (270-272) | 31 |
| **19** |  | 2 mmol A |  | 7 | 75 | 144-146 (145-146) | 29 |
| **20** |  | 2 mmol B |  | 6 | 85 | 290-292 (298-300) | 31 |
| **21** |  | 2 mmol A |  | 3 | 77 | 120-123 (128-130) | 30 |
| **22** |  | 2 mmol B |  | 5 | 85 | 210-212 (289-291) | 31 |

[a] Conditions: aldehyde (1 mmol), 1,3-dicarbonyl compounds (2 mmol), ammonium acetate (1.2 mmol) and catalyst (0.05 g) was used.
[b] Isolated yield

*J*= 6.9 Hz, 2 H. Ar-H),7.13 (d, *J*= 6.9 Hz, 1 H, Ar-H), 5.54(s, 1 H, NH), 4.99 (s, 1 H, CH), 4.09(q, *J* = 6.8 Hz, 4 H, 2 $OCH_2$), 2.34 (s, 6 H, 2 $CH_3$), 1.22 (t, *J* = 6.8 Hz, 6 H, 2 $CH_3CH_2$).

3,3,6,6-Tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione

(Entry 16, Table 4): Yellow solid. M.p. 240-242 ◦C. IR (KBr)/ū ($cm^{-1}$): 3274, 1642, 1480.$^1$H NMR ($CDCl_3$, 400 MHz/δ ppm: 7.33 (d, *J* = 7.5 Hz, 2 H, Ar-H), 7.19 (t, *J* = 7.5 Hz, 2 H, Ar- H), 7.07 (t, *J* = 7.5 Hz, 1 H, Ar-H), 6.68 (s, 1 H, NH), 5.08 (s, 1 H, CH), 2.14–2.39 (m, 8 H, 4 $CH_2$), 1.08 (s, 6 H, 2 $CH_3$), 0.97 (s, 6 H, 2 $CH_3$).

Diethyl-4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (Entry 17, Table 4): Yellow solid. M.p. 150-152 ◦C. IR (KBr)/ū ($cm^{-1}$): 3339, 1688, 1510, 1207. $^1$H NMR ($CDCl_3$, 400 MHz)/δ ppm: 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 $OCH_2$), 3.76 (s, 3 H, $OCH_3$), 2.33 (s, 6 H, 2 $CH_3$), 1.23 (t, *J* = 7.4 Hz, 6 H, 2 $CH_3CH_2$).

3,3,6,6-Tetramethyl-9-(4-methoxyphenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (Entry 18, Table 4): Yellow solid. M.p. 262-264 ◦C. IR (KBr)/ū ($cm^{-1}$): 3274, 1643, 1480, 1220. $^1$H NMR ($CDCl_3$, 400 MHz,)/δ ppm: 7.23 (d, *J* = 8.3 Hz, 2 H, Ar-H), 6.72 (d, *J* = 8.3 Hz, 2 H, Ar-H), 6.51 (s, 1 H, NH), 5.02 (s, 1 H, CH), 3.70 (s, 3 H, $OCH_3$), 2.14-2.37 (m, 8 H, 4 $CH_2$), 1.08 (s, 6 H, 2 $CH_3$), 0.96 (s, 6 H, 2 $CH_3$). $^{13}$C NMR ($CDCl_3$, 100 MHz)/δ ppm: 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.

Diethyl-4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (Entry 19, Table 4): Yellow solid. M.p: 144-146 ◦C. IR (KBr)/ū ($cm^{-1}$):

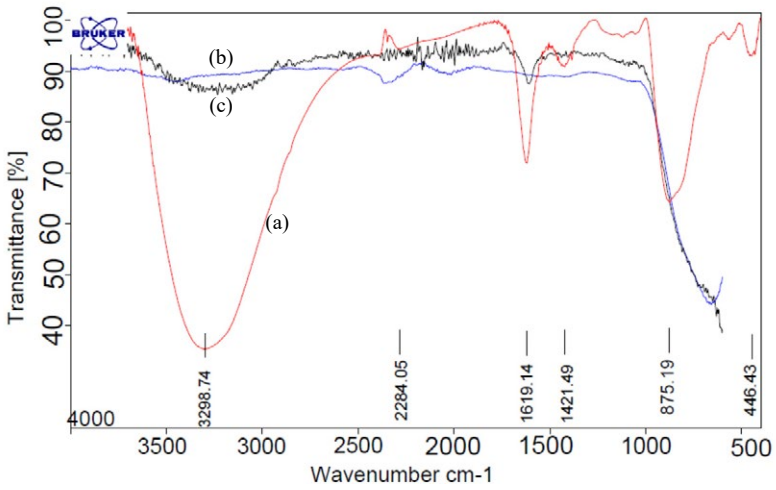



Fig. 1. FT-IR spectra of a) $TiCl_{4\,(aq)}$, b) nano-γ-$Al_2O_3$ and c) $TiCl_2$/nano-γ-$Al_2O_3$

3358, 1696, 1488, 1214, 1116. $^1$H NMR ($CDCl_3$, 400 MHz)/δ ppm: 7.22 (d, *J* = 8 Hz, 2 H. Ar-H), 7.17 (d, *J* = 8 Hz, 2 H, Ar-H), 5.55(s, 1 H, NH), 4.96 (s, 1 H, CH), 4.08(q, *J* = 7.2 Hz, 4 H, 2 $OCH_2$), 2.34 (s, 6 H, 2$CH_3$), 1.22 (t, *J* = 7.2 Hz, 6 H, 2$CH_3CH_2$).

3,3,6,6-Tetramethyl-9-(4-chlorophenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (Entry 20, Table 4): Yellowish solid. M.p. 290-292 °C. IR (KBr)/ū ($cm^{-1}$): 3174 , 1648, 1487, 1146. $^1$H NMR ($CDCl_3$, 400 MHz)/δ ppm: 7.27 (d, *J* = 8 Hz, 2 H, Ar-H), 7.17 (d, *J* = 8 Hz, 2 H, Ar-H), 6.79 (s, 1 H, NH), 5.05 (s, 1 H, CH), 2.13- 2.37 (m, 8 H, 4 $CH_2$), 1.08 (s, 6 H, 2 $CH_3$), 0.96 (s, 6 H, 2 $CH_3$).

Diethyl 2, 6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (Entry 21, Table 4): Orange solid. M.p. 120-123 °C. IR (KBr)/ū ($cm^{-1}$): 3316, 1699, 1516, 1485, 1344, 1208. $^1$H NMR ($CDCl_3$, 400 MHz)/δ ppm: 8.09 (d, *J* = 7.9 Hz, 2 H, Ar-H), 7.45 (d, *J* = 7.9 Hz, 2 H, Ar-H), 5.63 (s, 1 H, NH), 5.10 (s, 1 H,CH), 4.08 (q, *J* = 7.4 Hz, 4 H, 2 $OCH_2$), 2.37 (s, 6 H, 2$CH_3$), 1.24 (t, *J* = 7.4 Hz, 6 H, 2$CH_3CH_2$).$^{13}$C NMR ($CDCl_3$, 100 MHz)/δ ppm: 167.19, 155.28, 146.26, 144.99, 128.92, 123.30, 102.992, 60.02, 40.12, 19.53, 14.27.

3,3,6,6-Tetramethyl-9-(4-nitrophenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione

(Entry 22, Table 4): Brown-Orange solid. M.p. 210-212 °C. IR (KBr)/ū ($cm^{-1}$): 3385, 1643, 1513, 1477, 1344. $^1$H NMR ($CDCl_3$, 400 MHz)/δ ppm: 8.07 (d, *J* = 8.3 Hz, 2 H, Ar-H), 7.51(d, *J* = 8.3 Hz, 2 H, Ar-H), 6.13 (s, 1H, NH), 5.15 (s, 1 H, CH), 2.14- 2.45 (m, 8 H, 4 $CH_2$), 1.10 (s, 6 H, 2 $CH_3$), 0.96 (s, 6 H, 2 $CH_3$).

## RESULTS AND DISCUSSION

This research was performed in two steps. Firstly, $TiCl_2$/nano-γ-$Al_2O_3$ 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, $^1$HNMR, $^{13}$CNMR, spectroscopy.

For identification of the structure of $TiCl_2$/nano-γ-$Al_2O_3$, we have studied FT-IR (ATR) spectra of $TiCl_4$ (aq), nano-γ-$Al_2O_3$ and $TiCl_2$/nano-γ-$Al_2O_3$ (Fig. 2). In $TiCl_4$ (aq) spectrum, a broad band at 3298 ($H_2O$), a middle band at 1619 (Ti-Cl) and a strong band at 850 $cm^{-1}$ (Ti-O) were observed (Fig. 1a). In nano-γ-$Al_2O_3$ FT-IR spectrum, a very strong band at 600-1000$cm^{-1}$(Al-O) was observed (Fig. 1b). $TiCl_2$/nano-γ-$Al_2O_3$, in addition to γ-$Al_2O_3$ signal, two additional bands at 1619 and 3298 show binding of $TiCl_2$ to γ-$Al_2O_3$ (Fig. 1c).

The FE-SEM images of the $TiCl_2$/nano-γ-$Al_2O_3$ and nano-γ-$Al_2O_3$ nanoparticles are displayed in Fig. 2. They exhibit irregular spherical shape for nano particles below 50 nm.

Energy-Dispersive X-ray Spectroscopy (EDS) of $TiCl_2$/nano-γ-$Al_2O_3$ was measured by EDS instrument (Fig. 3) provided the presence of the expected elements in the structure of this catalyst and confirmed supporting of $TiCl_4$ on nano-γ-$Al_2O_3$. The elemental compositions of $TiCl_2$/nano-γ-$Al_2O_3$ were found to be 58.5, 29.9 and 6.5% for O, Al and

Ti, respectively.

To investigate the elemental component of $TiCl_2$/nano-γ-$Al_2O_3$, XRF analysis was performed. XRF analysis of catalyst was done by comparison of its Killo Counts per Seconds (KCPS) with pure samples. In our catalyst, $TiCl_2$/nano-γ-$Al_2O_3$, the percentage of elements, Ti, Cl and Al, were determined via comparison with KCPS of pure $TiO_2$, NaCl and $Al_2O_3$ 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 $TiCl_2$/nano-γ-$Al_2O_3$ 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-γ-$Al_2O_3$ 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-γ-$Al_2O_3$ (Fig. 4).

The specific surface area of catalyst was measured by Brunauer–Emmett–Teller (BET) theory. Single point surface area at P/Po =

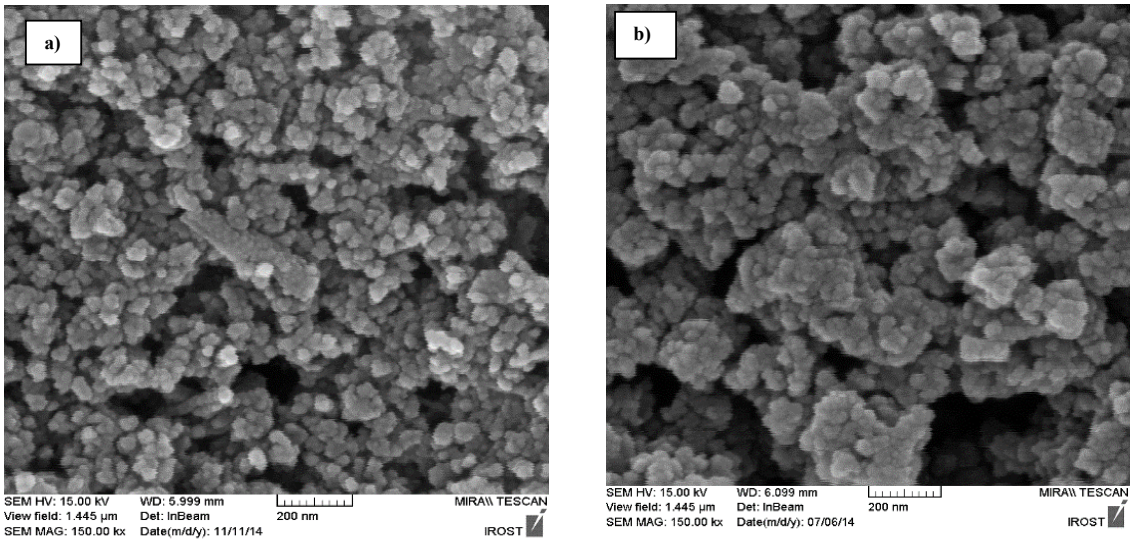



Fig . 2. The FESEM image of a) $TiCl_2$/nano-γ-$Al_2O_3$ and b) nano-γ-$Al_2O_3$

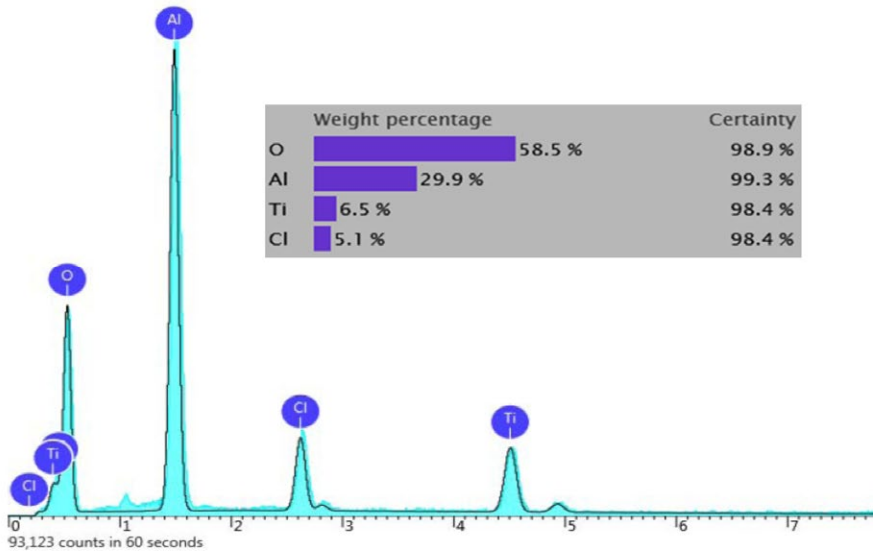



Fig. 3. EDS analysis diagram of $TiCl_2$/nano-γ-$Al_2O_3$

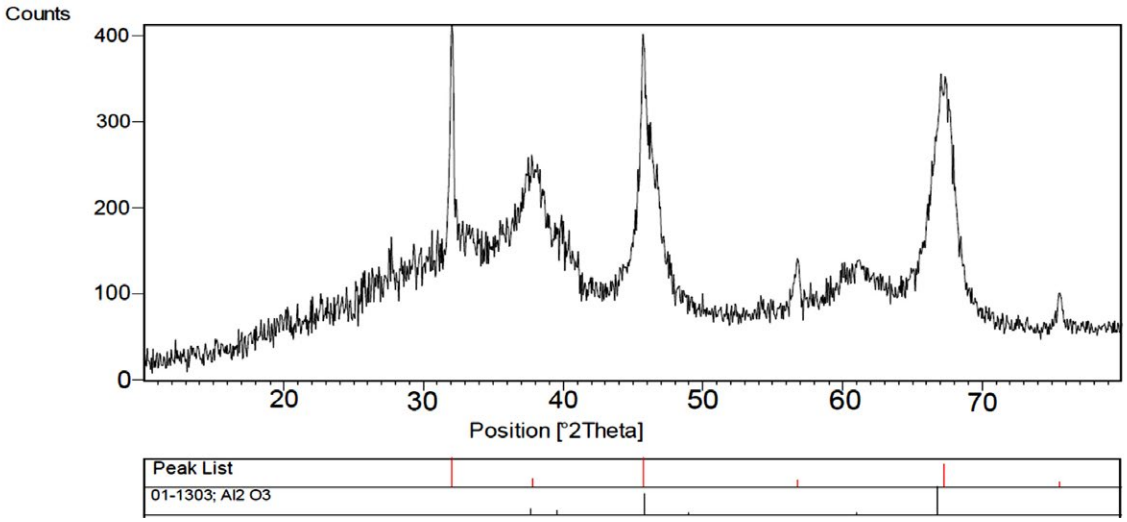



Fig. 4. XRD patterns of $TiCl_2$/nano-γ-$Al_2O_3$

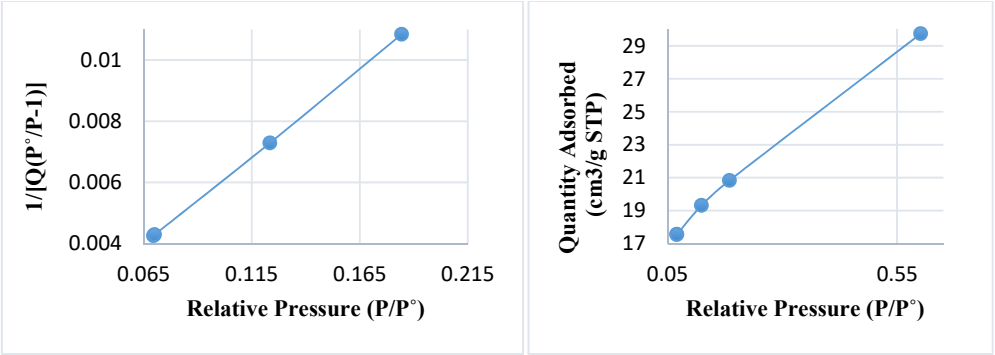



Fig. 5. Nitrogen adsorption isotherm at 77 K on $TiCl_2$/nano-γ-$Al_2O_3$

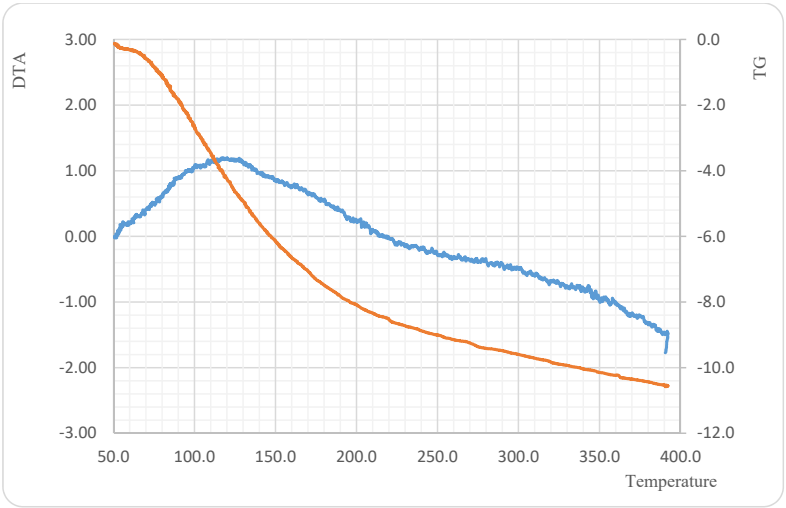



Fig. 6. Thermal gravimetric analysis (TG-DTG) pattern of $TiCl_2$/nano-γ-$Al_2O_3$

0.184317546 is 73.9645 m²/g and BET surface area is 75.5925 m²/g. The $N_2$ adsorption isotherm of catalyst is depicted in Fig. 5.

Thermal gravimetric analysis (TG-DTA) pattern of $TiCl_2$/nano-γ-$Al_2O_3$ 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 $TiCl_2$/nano-γ-$Al_2O_3$ 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 $TiCl_2$/nano-γ-$Al_2O_3$ (Fig. 7).

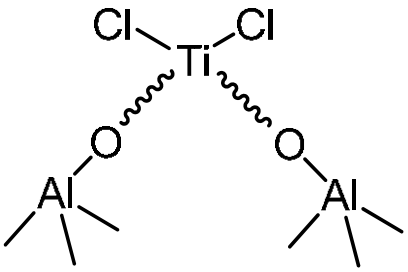



Fig. 7.The proposed structure for $TiCl_2$/nano-γ-$Al_2O_3$

For evaluation of the catalytic activity of $TiCl_2$/nano-γ-$Al_2O_3$, Initially, we have decided to explore the role of $TiCl_2$/nano-γ-$Al_2O_3$ for the synthesis of 1,4-dihydropyridines in a typical reaction to determine the optimum conditions. so 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 $TiCl_2$/nano-γ-$Al_2O_3$ 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 0.05g of $TiCl_2$/nano-γ-$Al_2O_3$ 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, $NO_2$, Cl, Br and $NH_2$ were converted to the corresponding 1,4-DHPs in good yields. Therefore $TiCl_2$/nano-γ-$Al_2O_3$ activates the carbonyl group of aldehyde as a Lewis acid in the synthesis of 1,4-DHPs.

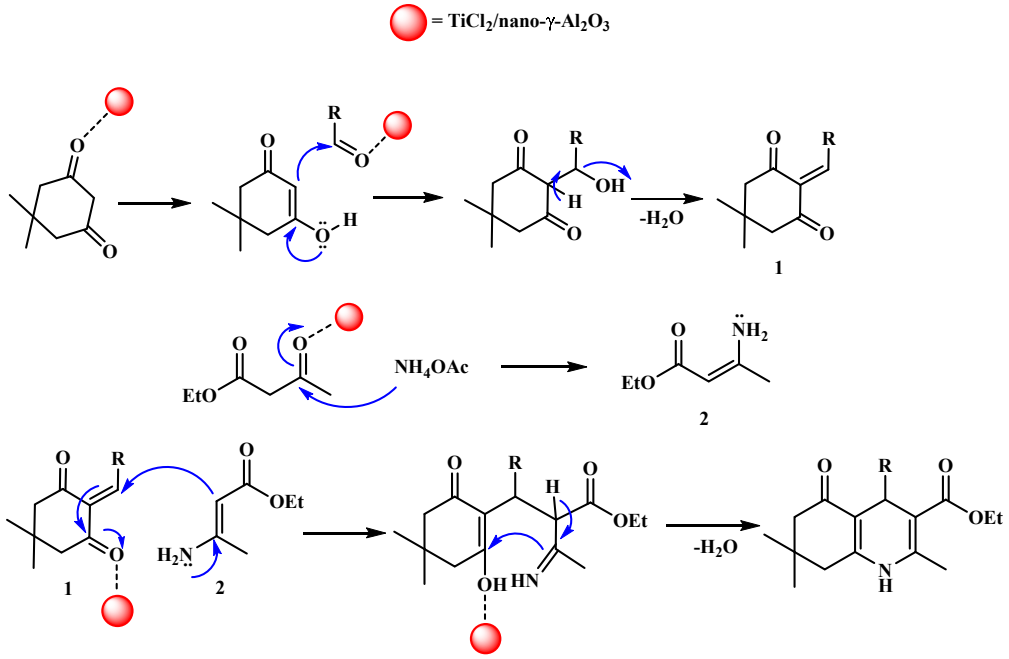



Fig. 8. Proposed mechanism for the synthesis of 1,4-dihydropyridines

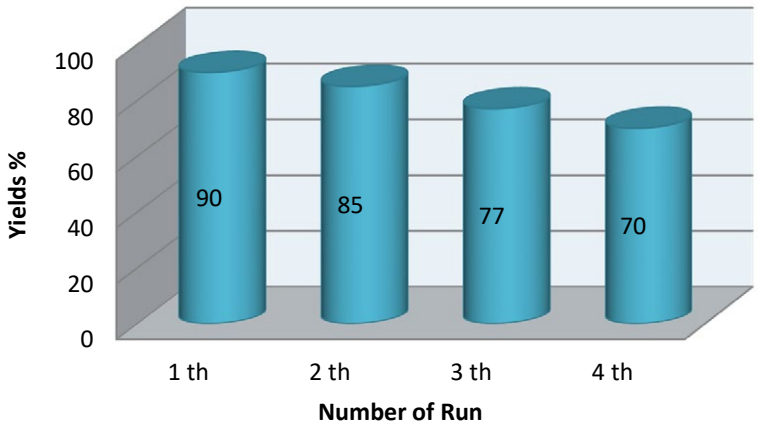



Fig. 9. Reusability investigation of $TiCl_2$/nano-γ-$Al_2O_3$ in 1,4-dihydropyridines synthesis

The proposed mechanism for the formation of 1,4-dihydropyridines in the presence of $TiCl_2$/nano-γ-$Al_2O_3$, which can act as Lewis acid catalyst (empty π orbital of Sn in $TiCl_2$/nano-γ-$Al_2O_3$) 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).

## CONCLUSION

In summary, we have developed a simple, efficient, and green protocol for synthesis of 1,4-dihydropyridines using $TiCl_2$/nano-γ-$Al_2O_3$ 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 Research Council of Yazd University is acknowledged for the financial support of this work.

## CONFLICTS OF INTEREST

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

## REFERENCES

1. Dömling A, Ugi I. Multicomponent Reactions with Isocyanides. Angewandte Chemie. 2000;39(18):3168-210.
2. Marques MV, Ruthner MM, Fontoura LAM, Russowsky D. Metal chloride hydrates as Lewis acid catalysts in multicomponent synthesis of 2,4,5-triarylimidazoles or 2,4,5-triaryloxazoles. Journal of the Brazilian Chemical Society. 2012;23(1):171-9.
3. Devi I, Bhuyan PJ. Sodium bromide catalysed one-pot synthesis of tetrahydrobenzo[b]pyrans via a three-component cyclocondensation under microwave irradiation and solvent free conditions. Tetrahedron Letters. 2004;45(47):8625-7.
4. Yang J, Jiang C, Yang J, Qian C, Fang D. A clean procedure for the synthesis of 1,4-dihydropyridines via Hantzsch reaction in water. Green Chemistry Letters and Reviews. 2013;6(3):262-7.
5. Hantzsch A. Ueber die Synthese pyridinartiger Verbindungen aus Acetessigäther und Aldehydammoniak. Justus Liebig's Annalen der Chemie. 1882;215(1):1-82.
6. Debache A, Ghalem W, Boulcina R, Belfaitah A, Rhouati S, Carboni B. An efficient one-step synthesis of 1,4-dihydropyridines via a triphenylphosphine-catalyzed three-component Hantzsch reaction under mild conditions. Tetrahedron Letters. 2009;50(37):5248-50.
7. Sirisha K, Bikshapathi D, Achaiah G, Reddy VM. Synthesis, antibacterial and antimycobacterial activities of some new 4-aryl/heteroaryl-2,6-dimethyl-3,5-bis-N-(aryl)-carbamoyl-1,4-dihydropyridines. European Journal of Medicinal Chemistry. 2011;46(5):1564-71.
8. Janis RA, Triggle DJ. New developments in calcium ion channel antagonists. Journal of Medicinal Chemistry. 1983;26(6):775-85.
9. Ghanta Mahesh R, Mehendra S, Akula Kalyan C. Chemical and Pharmacological Significance of 1,4-Dihydropyridines. Current Organic Chemistry. 2007;11(10):847-52.

10. Safari J, Banitaba SH, Khalili SD. Cellulose sulfuric acid catalyzed multicomponent reaction for efficient synthesis of 1,4-dihydropyridines via unsymmetrical Hantzsch reaction in aqueous media. Journal of Molecular Catalysis A: Chemical. 2011;335(1-2):46-50.
11. Godfraind T, Miller R, Wibo M. Calcium antagonism and calcium entry blockade. Pharmacological Reviews. 1986;38(4):321-416.
12. Triggle DJ. Calcium channel antagonists: Clinical uses—Past, present and future. Biochemical Pharmacology. 2007;74(1):1-9.
13. Zare L, Nikpassand M. Multicomponent synthesis of dihydropyridines catalyzed by l-proline. Chinese Chemical Letters. 2011;22(5):531-4.
14. Bahekar S, Shinde D. Synthesis and anti-inflammatory activity of 1-4-dihydropyridines2002. 281-287 p.
15. Wächter GA, Davis MC, Martin AR, Franzblau SG. Antimycobacterial Activity of Substituted Isosteres of Pyridine- and Pyrazinecarboxylic Acids. Journal of Medicinal Chemistry. 1998;41(13):2436-8.
16. Gullapalli S, Ramarao P. L-type Ca2+ channel modulation by dihydropyridines potentiates κ-opioid receptor agonist induced acute analgesia and inhibits development of tolerance in rats. Neuropharmacology. 2002;42(4):467-75.
17. Sunkel CE, Fau de Casa-Juana M, Santos L, Mar Gomez M, Villarroya M, Gonzalez-Morales MA, et al. 4-Alkyl-1,4-dihydropyridine derivatives as specific PAF-acether antagonists. Journal of Medicinal Chemistry. 1990;33(12):3205-10.
18. M. O. Handkinura, Drug Res. 3 (1981) 1131-1134.
19. Triggle DJ. Cellular and Molecular Neurobiology. 2003;23(3):293-303.
20. Goldmann S, Stoltefuss J. 1,4-Dihydropyridines: Effects of Chirality and Conformation on the Calcium Antagonist and Calcium Agonist Activities. Angewandte Chemie International Edition in English. 1991;30(12):1559-78.
21. Polshettiwar V, Varma RS. Green chemistry by nano-catalysis. Green Chemistry. 2010;12(5):743.
22. Nasr-Esfahani M, Hoseini SJ, Montazerozohori M, Mehrabi R, Nasrabadi H. Magnetic Fe3O4 nanoparticles: Efficient and recoverable nanocatalyst for the synthesis of polyhydroquinolines and Hantzsch 1,4-dihydropyridines under solvent-free conditions. Journal of Molecular Catalysis A: Chemical. 2014;382:99-105.
23. Baghbanian SM, Khaksar S, Vahdat SM, Farhang M, Tajbakhsh M. One-step, synthesis of Hantzsch esters and polyhydroquinoline derivatives using new organocatalyst. Chinese Chemical Letters. 2010;21(5):563-7.
24. Wang L-M, Sheng J, Zhang L, Han J-W, Fan Z-Y, Tian H, et al. Facile Yb(OTf)3 promoted one-pot synthesis of polyhydroquinoline derivatives through Hantzsch reaction. Tetrahedron. 2005;61(6):1539-43.
25. Ko S, Sastry MNV, Lin C, Yao C-F. Molecular iodine-catalyzed one-pot synthesis of 4-substituted-1,4-dihydropyridine derivatives via Hantzsch reaction. Tetrahedron Letters. 2005;46(34):5771-4.
26. Sapkal SB, Shelke KF, Shingate BB, Shingare MS. Nickel nanoparticle-catalyzed facile and efficient one-pot synthesis of polyhydroquinoline derivatives via Hantzsch condensation under solvent-free conditions. Tetrahedron Letters. 2009;50(15):1754-6.
27. Mansoor SS, Aswin K, Logaiya K, Sudhan PN, Malik S. Silica-supported perchloric acid (HClO4–SiO2): a mild, reusable and highly efficient heterogeneous catalyst for multicomponent synthesis of 1,4-dihydropyridines via unsymmetrical Hantzsch reaction. Research on Chemical Intermediates. 2012;40(1):357-69.
28. Vahdat SM, Chekin F, Hatami M, Khavarpour M, Baghery S, Roshan-Kouhi Z. Synthesis of polyhydroquinoline derivatives via a four-component Hantzsch condensation catalyzed by tin dioxide nanoparticles. Chinese Journal of Catalysis. 2013;34(4):758-63.
29. Wang S-X, Li Z-Y, Zhang J-C, Li J-T. The solvent-free synthesis of 1,4-dihydropyridines under ultrasound irradiation without catalyst. Ultrasonics Sonochemistry. 2008;15(5):677-80.
30. Tajbakhsh M, Alaee E, Alinezhad H, Khanian M, Jahani F, Khaksar S, et al. Titanium Dioxide Nanoparticles Catalyzed Synthesis of Hantzsch Esters and Polyhydroquinoline Derivatives. Chinese Journal of Catalysis. 2012;33(9-10):1517-22.
31. Dam B, Nandi S, Pal AK. An efficient 'on-water' synthesis of 1,4-dihydropyridines using Fe3O4@SiO2 nanoparticles as a reusable catalyst. Tetrahedron Letters. 2014;55(38):5236-40.