

## Metal oxide nanoparticles as reusable heterogeneous catalysts in the synthesis of 1,4-dihydropyridine derivatives via solvent-free Hantzsch reaction: A comparative study

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**Abstract:** The catalytic effect of three nano-sized metal oxides including  $\text{Al}_2\text{O}_3$ ,  $\text{Fe}_3\text{O}_4$ , and  $\text{TiO}_2$  nanoparticles, in the synthesis of 1,4-Dihydropyridines by one-pot three-component reaction of aliphatic\aromatic aldehydes, ammonium acetate, and ethyl acetoacetate, has been investigated. Different reaction conditions were studied in the presence of  $\text{Al}_2\text{O}_3$ ,  $\text{Fe}_3\text{O}_4$ , and  $\text{TiO}_2$  nanoparticles as catalysts. The results showed that nano  $\text{TiO}_2$  acts as more effective heterogeneous catalyst than others and the reaction proceeded more easily and gave the highest yields of the products in shorter reaction times under thermal solvent-free conditions. Short reaction times, simple isolation of the products, and usage of eco-friendly catalysts are some features of this procedure. In addition, the catalysts were easily recovered and used in multiple catalytic cycles.

**Keywords:** Comparative study, Metal oxide nanoparticles, 1,4-Dihydropyridines, Solvent-free synthesis.

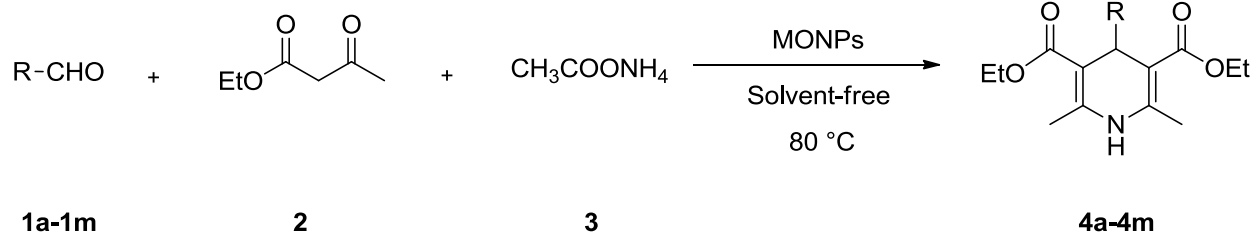
### Introduction

The problems associated with most homogeneous catalysts, such as their environmental hazards and difficult recovery, have increased the interest to develop alternative procedures using heterogeneous ones[1–3]. The potential advantages of heterogeneous catalysts could potentially allow for the development of environmentally benign processes in both academic and industrial settings[4–6]. In recently years, among the various heterogeneous catalysts, nanoparticles have attracted much attention for their high surface area[7,8]. As the particle size decreases, ample external surface area emerged, which allows the accessibility to a large amount of the active centers, and thus the activity of the catalyst increases.

Despite various compounds have been synthesized and tested as catalysts in organic transformations[9–21], there have been no reports toward the use of three important metal oxide nanoparticles (MONPs) such as  $\text{Al}_2\text{O}_3$ ,  $\text{Fe}_3\text{O}_4$  and  $\text{TiO}_2$  as catalysts for the synthesis of 1,4-Dihydropyridines, an important class of organic compounds with diverse and interesting biological activities. These compounds are synthesized via the one-pot three-component reaction of aldehyde, ammonium acetate, and ethyl acetoacetate using various homogeneous and heterogeneous catalysts [22–36].

As part of our research program on the development of convenient methods using reusable catalysts for the synthesis of organic compounds [37–42]. We report here the results of our investigation on the application of  $\text{Al}_2\text{O}_3$ ,  $\text{Fe}_3\text{O}_4$  and  $\text{TiO}_2$  nanoparticles as heterogeneous catalysts in the synthesis of 1,4-Dihydropyridines (Scheme 1).

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**Scheme 1:** Nano metal oxides catalyzed synthesis of 1,4-Dihydropyridines

## Result and Discussion

First, the reaction between 4-chlorobenzaldehyde **1b** (1 mmol), ethyl acetoacetate **2** (2 mmol), and ammonium acetate **3** (1 mmol) for the synthesis of compound **4b** was selected as the test reaction and optimized with different nano metal oxide catalysts in terms of various parameters like catalyst amount, effect of solvent, and influence of temperature. A summary of the optimization experiments is provided in Table 1. As seen, although all used nano metal oxide catalysts show good catalytic effects in the model reaction, but  $\text{TiO}_2$  nanoparticles improve the reaction more effectively than others, obtaining higher yields of **4b**. For finding the best catalyst amount, we started the experiments using 0.02 g of each catalyst. Moderate yields of the product were obtained in this condition. Increasing the amount of each of the catalysts increased the yields of the product **4b**. The optimal amount was 0.10 g (Entry 16) under solvent-free conditions; increasing the amount of the catalyst beyond this value had no significant effect on the

yields and reaction times. Subsequently, the effect of different solvents on the reaction rate as well as the product yield was investigated. As can be seen from Table 1, for all used catalysts, the best results were achieved under solvent-free conditions. The effect of temperature on the reaction was also studied in the same model reaction. It was observed that the yield increased as the reaction temperature was raised, and at  $80^\circ\text{C}$  the product **4b** was obtained in excellent yield. Moreover, to substantiate the important role of the catalyst, the reaction was carried out at  $80^\circ\text{C}$  in the absence of the catalyst under solvent-free conditions (Entry 1). As a result, only low yield of the product was formed, indicating that the catalyst is necessary for the reaction. Thereafter, the applicability of the method was evaluated for the synthesis of other 1,4-Dihydropyridines using a wide range of aliphatic/aromatic aldehydes. Our observations are recorded on Table 2.  $\text{TiO}_2$  nanoparticles proved to be the better catalyst than nano-sized  $\text{Fe}_3\text{O}_4$  and  $\text{Al}_2\text{O}_3$  in terms of yield and reaction time.

**Table 1:** Synthesis of compound **4b** in the presence of the  $\text{Al}_2\text{O}_3$ ,  $\text{Fe}_3\text{O}_4$  and  $\text{TiO}_2$  nanoparticles as catalysts under different reaction conditions.

Entry	Nano metal oxide	Catalyst amount (g)	Solvent	T ( $^\circ\text{C}$ )	Time (min)	Yield* (%)
1	-----	-----	-----	80	150	18
2	$\text{Al}_2\text{O}_3/\text{Fe}_3\text{O}_4/\text{TiO}_2$	0.02	-----	40	60/60/55	39/41/45
3	$\text{Al}_2\text{O}_3/\text{Fe}_3\text{O}_4/\text{TiO}_2$	0.02	-----	60	55/55/50	43/43/49
4	$\text{Al}_2\text{O}_3/\text{Fe}_3\text{O}_4/\text{TiO}_2$	0.02	-----	80	45/45/45	48/51/57
5	$\text{Al}_2\text{O}_3/\text{Fe}_3\text{O}_4/\text{TiO}_2$	0.04	-----	40	40/45/40	52/59/62
6	$\text{Al}_2\text{O}_3/\text{Fe}_3\text{O}_4/\text{TiO}_2$	0.04	-----	60	35/35/30	58/65/70
7	$\text{Al}_2\text{O}_3/\text{Fe}_3\text{O}_4/\text{TiO}_2$	0.04	-----	80	35/35/30	60/67/73

8	Al <sub>2</sub> O <sub>3</sub> /Fe <sub>3</sub> O <sub>4</sub> /TiO <sub>2</sub>	0.06	-----	40	30/25/25	68/69/77
9	Al <sub>2</sub> O <sub>3</sub> /Fe <sub>3</sub> O <sub>4</sub> /TiO <sub>2</sub>	0.06	-----	60	25/25/25	70/72/79
10	Al <sub>2</sub> O <sub>3</sub> /Fe <sub>3</sub> O <sub>4</sub> /TiO <sub>2</sub>	0.06	-----	80	25/25/20	73/75/82
11	Al <sub>2</sub> O <sub>3</sub> /Fe <sub>3</sub> O <sub>4</sub> /TiO <sub>2</sub>	0.08	-----	40	22/22/20	75/79/85
12	Al <sub>2</sub> O <sub>3</sub> /Fe <sub>3</sub> O <sub>4</sub> /TiO <sub>2</sub>	0.08	-----	60	20/20/20	78/83/88
13	Al <sub>2</sub> O <sub>3</sub> /Fe <sub>3</sub> O <sub>4</sub> /TiO <sub>2</sub>	0.08	-----	80	20/20/20	80/83/90
14	Al <sub>2</sub> O <sub>3</sub> /Fe <sub>3</sub> O <sub>4</sub> /TiO <sub>2</sub>	0.10	-----	40	20/20/18	84/86/92
15	Al <sub>2</sub> O <sub>3</sub> /Fe <sub>3</sub> O <sub>4</sub> /TiO <sub>2</sub>	0.10	-----	60	20/20/18	86/89/94
16	Al <sub>2</sub> O <sub>3</sub> /Fe <sub>3</sub> O <sub>4</sub> /TiO <sub>2</sub>	0.10	-----	80	20/18/16	89/93/96
17	Al <sub>2</sub> O <sub>3</sub> /Fe <sub>3</sub> O <sub>4</sub> /TiO <sub>2</sub>	0.12	-----	40	25/25/20	78/82/84
18	Al <sub>2</sub> O <sub>3</sub> /Fe <sub>3</sub> O <sub>4</sub> /TiO <sub>2</sub>	0.12	-----	60	20/20/20	81/86/88
19	Al <sub>2</sub> O <sub>3</sub> /Fe <sub>3</sub> O <sub>4</sub> /TiO <sub>2</sub>	0.12	-----	80	20/18/18	84/87/93
20	Al <sub>2</sub> O <sub>3</sub> /Fe <sub>3</sub> O <sub>4</sub> /TiO <sub>2</sub>	0.10	-----	100	25/25/20	86/89/95
21	Al <sub>2</sub> O <sub>3</sub> /Fe <sub>3</sub> O <sub>4</sub> /TiO <sub>2</sub>	0.10	EtOH	Reflux	120/120/100	68/69/73
22	Al <sub>2</sub> O <sub>3</sub> /Fe <sub>3</sub> O <sub>4</sub> /TiO <sub>2</sub>	0.10	MeOH	Reflux	120/120/100	54/57/65
23	Al <sub>2</sub> O <sub>3</sub> /Fe <sub>3</sub> O <sub>4</sub> /TiO <sub>2</sub>	0.10	CH <sub>2</sub> Cl <sub>2</sub>	Reflux	120/120/100	29/35/45
24	Al <sub>2</sub> O <sub>3</sub> /Fe <sub>3</sub> O <sub>4</sub> /TiO <sub>2</sub>	0.10	CH <sub>3</sub> CN	Reflux	120/120/100	40/45/53
25	Al <sub>2</sub> O <sub>3</sub> /TiO <sub>2</sub> /Fe <sub>3</sub> O <sub>4</sub>	0.10	CH <sub>3</sub> CO <sub>2</sub> Et	Reflux	120/120/100	27/33/43

Reaction conditions: 4-chlorobenzaldehyde **1b** (1 mmol), ethyl acetoacetate **2** (2 mmol), and ammonium acetate **3** (1 mmol).  
\*Isolated yields.

**Table 2.** Synthesis of 1,4-Dihydropyridines **4a-m**, catalyzed by MONPs

Comp. no	Ar	Catalyst	Time (min)	Yield* (%)
<b>4a</b>	C <sub>6</sub> H <sub>5</sub>	Al <sub>2</sub> O <sub>3</sub> /Fe <sub>3</sub> O <sub>4</sub> /TiO <sub>2</sub>	28/25/22	85/92/94
<b>4b</b>	4-ClC <sub>6</sub> H <sub>4</sub>	Al <sub>2</sub> O <sub>3</sub> /Fe <sub>3</sub> O <sub>4</sub> /TiO <sub>2</sub>	20/18/16	89/93/96
<b>4c</b>	3-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	Al <sub>2</sub> O <sub>3</sub> /Fe <sub>3</sub> O <sub>4</sub> /TiO <sub>2</sub>	27/25/23	86/89/93
<b>4d</b>	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	Al <sub>2</sub> O <sub>3</sub> /Fe <sub>3</sub> O <sub>4</sub> /TiO <sub>2</sub>	20/20/17	81/85/92
<b>4e</b>	4-MeC <sub>6</sub> H <sub>4</sub>	Al <sub>2</sub> O <sub>3</sub> /Fe <sub>3</sub> O <sub>4</sub> /TiO <sub>2</sub>	25/20/15	88/92/97

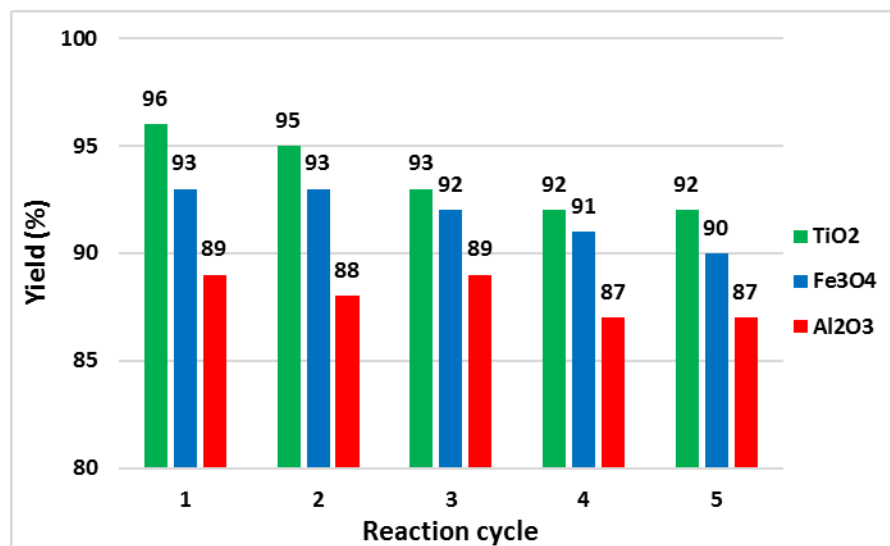
<b>4f</b>	4-MeOC <sub>6</sub> H <sub>4</sub>	Al <sub>2</sub> O <sub>3</sub> /Fe <sub>3</sub> O <sub>4</sub> /TiO <sub>2</sub>	20/17/14	89/91/95
<b>4g</b>	4-HOC <sub>6</sub> H <sub>4</sub>	Al <sub>2</sub> O <sub>3</sub> /Fe <sub>3</sub> O <sub>4</sub> /TiO <sub>2</sub>	30/25/20	80/86/89
<b>4h</b>	4-BrC <sub>6</sub> H <sub>4</sub>	Al <sub>2</sub> O <sub>3</sub> /Fe <sub>3</sub> O <sub>4</sub> /TiO <sub>2</sub>	25/25/20	87/90/93
<b>4i</b>	3-BrC <sub>6</sub> H <sub>4</sub>	Al <sub>2</sub> O <sub>3</sub> /Fe <sub>3</sub> O <sub>4</sub> /TiO <sub>2</sub>	23/18/13	85/91/93
<b>4j</b>	4-FC <sub>6</sub> H <sub>4</sub>	Al <sub>2</sub> O <sub>3</sub> /Fe <sub>3</sub> O <sub>4</sub> /TiO <sub>2</sub>	23/20/17	80/85/90
<b>4k</b>	2-Thienyl	Al <sub>2</sub> O <sub>3</sub> /Fe <sub>3</sub> O <sub>4</sub> /TiO <sub>2</sub>	25/20/16	88/91/96
<b>4l</b>	Et	Al <sub>2</sub> O <sub>3</sub> /Fe <sub>3</sub> O <sub>4</sub> /TiO <sub>2</sub>	20/20/14	79/84/89
<b>4m</b>	n-propyl	Al <sub>2</sub> O <sub>3</sub> /Fe <sub>3</sub> O <sub>4</sub> /TiO <sub>2</sub>	25/20/15	81/86/90

Reaction conditions: 4-chlorobenzaldehyde **1b** (1 mmol), ethyl acetoacetate **2** (2 mmol), and ammonium acetate **3** (1 mmol), nano metal oxide (0.10 g), 80 °C, solvent-free. \* Isolated yields.

On the other hand, the reusability of three nano catalysts in model reaction was also investigated. For this purpose, after separation of the catalyst according to the procedure outlined in the experimental section, the recovered catalysts were washed with hot ethanol and subsequently dried at 60 °C under vacuum for 1 h before being reused in a similar reaction. All the three catalysts could be used at least five times without significant reduction in its activity (89/93/96, 88/93/95, 89/92/93, 87/91/92 and 87/90/92% yields for nano Al<sub>2</sub>O<sub>3</sub>/Fe<sub>3</sub>O<sub>4</sub>/TiO<sub>2</sub> catalysts in first to fifth use,

respectively) which clearly demonstrates the practical reusability of these catalysts (Fig. 1).

The applicability and efficiency of our catalysts were compared with some of the reported methods for the synthesis of 1,4-Dihydropyridines. This comparison is shown in Table 3. It is clear from the data that our procedure with nano TiO<sub>2</sub> as catalyst gave high yields of the products in shorter reaction times than the other conditions.



**Figure 1:** Effect of recycling on catalytic performance of Al<sub>2</sub>O<sub>3</sub>, Fe<sub>3</sub>O<sub>4</sub> and TiO<sub>2</sub> in the synthesis of **4b** in model reaction.

**Table 3:** Comparison of the efficiencies of different catalysts for the one-pot three-component synthesis of 1,4-DHPs.

Catalyst	Conditions			Time (min)	Yield (%)	Ref.
	Solvent	T/°C	Other			
TMSCL-NaI	CH <sub>3</sub> CN	r.t	----	360-480	73-80	[22]
VB <sub>1</sub>	----	r.t	----	40	80-94	[23]
SiO <sub>2</sub> -NaHSO <sub>4</sub>	----	r.t	----	300-480	75-90	[24]
PEG-400	----	90	----	240-420	75-95	[25]
silica sulfuric acid	----	r.t	----	15-45	90-97	[26]
CeCl <sub>3</sub> ·7H <sub>2</sub> O	CH <sub>3</sub> CN	r.t	----	180-360	61-94	[27]
Salicylic Acid	----	80	----	120	64-89	[28]
Iodine (I <sub>2</sub> )	----	40	----	45-300	64-89	[29]
PPh <sub>3</sub>	EtOH	reflux	----	120-300	72-95	[30]
<i>t</i> -BuOK	----	60	----	120-600	23-84	[31]
Cellulose sulfuric acid	----	100	----	120-300	78-92	[32]
PDAG-Co	----	80	----	360-480	75-99	[33]
SiO <sub>2</sub> -NaHSO <sub>4</sub>	----	r.t	----	300-480	75-90	[34]
TBAHS	----	80	----	30-90	90-98	[35]
[PS-IM(CH <sub>2</sub> ) <sub>4</sub> SO <sub>3</sub> H][HSO <sub>4</sub> ]	EtOH	reflux	----	120-210	80-95	[36]
Al <sub>2</sub> O <sub>3</sub> Nanoparticles	---	80	---	20-30	79-89	This work
Fe <sub>3</sub> O <sub>4</sub> Nanoparticles	---	80	---	17-23	84-93	This work
TiO <sub>2</sub> Nanoparticles	---	80	---	13-20	89-97	This work

Plausible mechanism for this reaction may proceed as depicted in Scheme 2. Al<sub>2</sub>O<sub>3</sub>, Fe<sub>3</sub>O<sub>4</sub>, and TiO<sub>2</sub> nanoparticles could act as Lewis acid and therefore promote the necessary reactions. These catalysts would play a significant role in increasing the electrophilic character of the electrophiles in the reaction. According to this mechanism, catalysts would facilitate the formation of intermediates I, II, and III. Under these conditions, however, attempts to isolate the proposed intermediates failed even after careful monitoring of the reactions.

## Conclusions

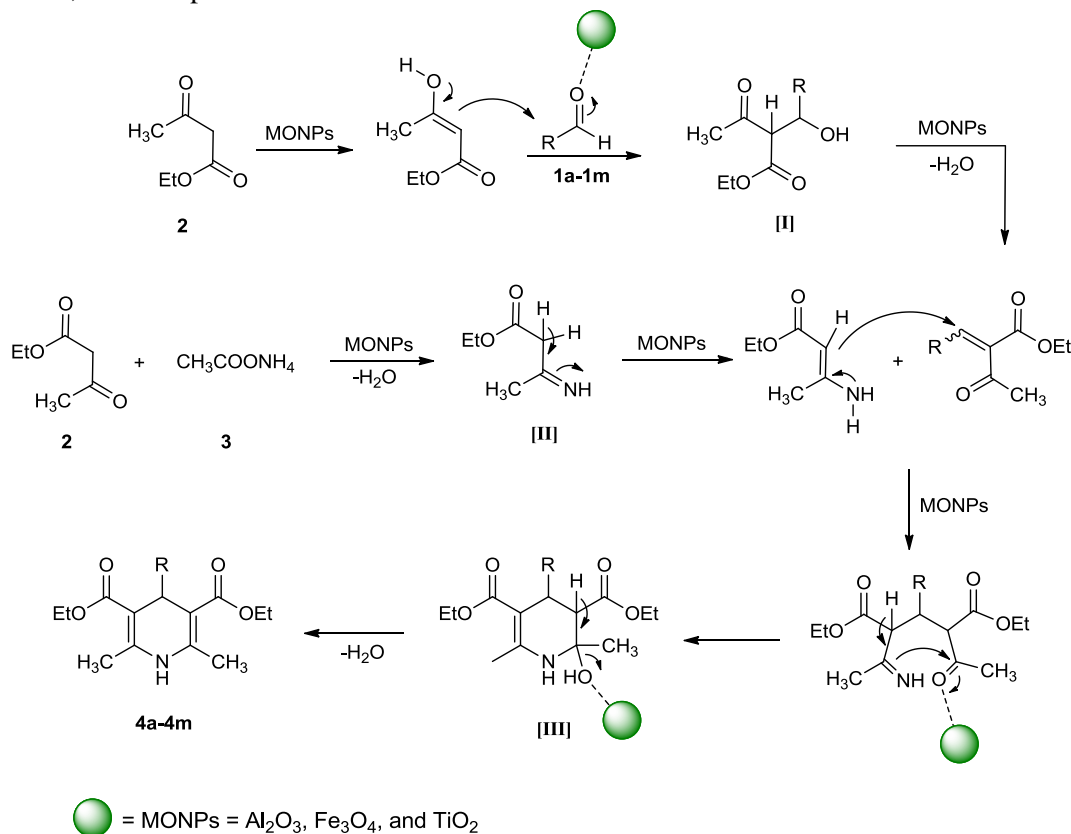
In conclusion, the catalytic activity of three commercially available nano-sized metal oxides including Al<sub>2</sub>O<sub>3</sub>, Fe<sub>3</sub>O<sub>4</sub>, and TiO<sub>2</sub> were compared in the synthesis of 1,4-Dihydropyridines by one-pot three-component reaction of aldehyde, ethyl acetoacetate, and ammonium acetate. The reactions proceeded under solvent-free conditions at 80 °C giving the high yields of the products in short reaction times. Among the three tested nano catalysts, TiO<sub>2</sub> nanoparticles proved

to be the better catalyst than others in terms of yield, reaction time, and easy separation. Some attractive features of these protocols are high yields, short reaction times, easy work-up, high catalytic activity and recyclability and reusability of the catalyst. The catalysts could be used at least five times without substantial reduction in their catalytic activities.

## Experimental

Nano-sized metal oxides,  $\text{Al}_2\text{O}_3$ ,  $\text{Fe}_3\text{O}_4$ , and  $\text{TiO}_2$  nanoparticles, were purchased from Tecnan

Spanish Company. All of the other chemicals were purchased from Merck and Aldrich and used without purification. The IR spectra were obtained using a Tensor 27 Bruker spectrophotometer in KBr disks. The  $^1\text{H}$  NMR spectra were recorded on Bruker 400 and 500 spectrometers. The melting points were measured on a Stuart SMP3 melting point apparatus.



**Scheme 2:** Plausible mechanism for the MONPs catalyzed formation of 1,4-DHPs.

### General procedure for the synthesis of 1,4-Dihydropyridines 4a-4m catalyzed by nano-sized metal oxides.

A mixture of aldehyde **1a-1m** (1 mmol), ethyl acetoacetate **2** (2 mmol), ammonium acetate **3** (1 mmol), and a nano-sized metal oxide (0.10 g) was heated in an oil bath at  $80\text{ }^\circ\text{C}$ . The reaction was monitored by TLC. Upon completion of the transformation, the reaction mixture was cooled to room temperature and hot ethanol was added. This resulted in the precipitation of the catalyst, which was collected by filtration (for  $\text{TiO}_2$ , and  $\text{Al}_2\text{O}_3$  nanoparticles) or using an external magnet (for  $\text{Fe}_3\text{O}_4$

nanoparticles). The product was collected from the filtrate after cooling to room temperature and recrystallized from ethanol to give compounds **4a-4m** in high yields. The separated catalyst was washed with hot ethanol, dried at  $60\text{ }^\circ\text{C}$  under vacuum for 1 h and reused for the same experiment. Purity checks with melting points, TLC and the  $^1\text{H}$  NMR spectroscopic data reveal that only one product is formed in all cases and no undesirable side-products are observed. The structures of all known products **4a-4m** were deduced from their  $^1\text{H}$  NMR and FT-IR spectral data and a comparison of their melting points with those of authentic samples.

**Diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (4a):**

M.p.: 154-156 °C (lit. [25] 156-158 °C); FT-IR ( $\nu$ ,  $\text{cm}^{-1}$  KBr disc): 3342, 3061, 2982, 1688, 1651, 1489, 1372, 1211, 1167, 828;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.25 (t,  $J = 7.1$  Hz, 6H, 2 $\text{CH}_3$ ), 2.37 (s, 6H, 2 $\text{CH}_3$ ), 4.05-4.18 (m, 4H, 2 $\text{CH}_2$ , diastereotopic protons), 5.02 (s, 1H, CH), 5.58 (s br., 1H, NH), 7.10-7.35 (m, 5H, aromatic CH).

**Diethyl 4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4b):**

M.p.: 149-151 °C (lit. [25] 148-150 °C); FT-IR ( $\nu$ ,  $\text{cm}^{-1}$  KBr disc): 3358, 3094, 2987, 1696, 1651, 1487, 1334, 1213, 1118, 1094, 843;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.25 (t,  $J = 7.1$  Hz, 6H, 2 $\text{CH}_3$ ), 2.36 (s, 6H, 2 $\text{CH}_3$ ), 4.05-4.18 (m, 4H, 2 $\text{CH}_2$ , diastereotopic protons), 4.99 (s, 1H, CH), 5.66 (s br., 1H, NH), 7.20 (d,  $J = 8.3$  Hz, 2H, aromatic CH), 7.24 (d,  $J = 8.3$  Hz, 2H, aromatic CH).

**Diethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4c):**

M.p.: 163-165 °C (lit. [25] 162-164 °C); FT-IR ( $\nu$ ,  $\text{cm}^{-1}$  KBr disc): 3346, 3091, 2991, 1706, 1646, 1525, 1488, 1446, 1371, 1348, 1301, 1214, 1119, 1052, 879;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.25 (t,  $J = 7.1$  Hz, 6H, 2 $\text{CH}_3$ ), 2.40 (s, 6H, 2 $\text{CH}_3$ ), 4.05-4.20 (m, 4H, 2 $\text{CH}_2$ , diastereotopic protons), 5.13 (s, 1H, CH), 5.75 (s br., 1H, NH), 7.40 (t,  $J = 7.9$  Hz, 1H, aromatic CH), 7.67 (dt,  $J = 7.7, 1.3$  Hz, 1H, aromatic CH), 8.03 (ddd,  $J = 8.2, 2.3, 1.0$  Hz, 1H, aromatic CH), 8.16 (t,  $J = 1.9$  Hz, 1H, aromatic CH).

**Diethyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4d):**

M.p.: 132-134 °C (lit. [25] 130-132 °C); FT-IR ( $\nu$ ,  $\text{cm}^{-1}$  KBr disc): 3345, 3090, 2991, 1706, 1645, 1525, 1487, 1347, 1213, 1118, 1051, 879;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , ppm):  $\delta$  1.25 (t,  $J = 7.1$  Hz, 6H, 2 $\text{CH}_3$ ), 2.39 (s, 6H, 2 $\text{CH}_3$ ), 4.05-4.18 (m, 4H, 2 $\text{CH}_2$ , diastereotopic protons), 5.13 (s, 1H, CH), 5.72 (s br., 1H, NH), 7.48 (d,  $J = 8.7$  Hz, 2H, aromatic CH), 8.11 (d,  $J = 8.7$  Hz, 2H, aromatic CH).

**Diethyl 2,6-dimethyl-4-(4-methylphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4e):**

M.p.: 135-137 °C (lit. [30] 136-138 °C); FT-IR ( $\nu$ ,  $\text{cm}^{-1}$  KBr disc): 3336, 3069, 2959, 1651, 1606, 1492, 1398, 1366, 1222, 1146;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.26 (t,  $J = 7.1$  Hz, 6H, 2 $\text{CH}_3$ ), 2.31 (s, 3H,

$\text{CH}_3$ ), 2.36 (s, 6H, 2 $\text{CH}_3$ ), 4.05-4.18 (m, 4H, 2 $\text{CH}_2$ , diastereotopic protons), 4.99 (s, 1H, CH), 5.60 (s br., 1H, NH), 7.04 (d,  $J = 7.8$  Hz, 2H, aromatic CH), 7.20 (d,  $J = 7.8$  Hz, 2H, aromatic CH).

**Diethyl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4f):**

M.p.: 158-160 °C (lit. [25] 159-160 °C); FT-IR ( $\nu$ ,  $\text{cm}^{-1}$  KBr disc): 3342, 3089, 2984, 1689, 1650, 1509, 1490, 1372, 1338, 1210, 1140, 1031, 834;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.26 (t,  $J = 7.1$  Hz, 6H, 2 $\text{CH}_3$ ), 2.36 (s, 6H, 2 $\text{CH}_3$ ), 3.79 (s, 3H,  $\text{OCH}_3$ ), 4.05-4.20 (m, 4H, 2 $\text{CH}_2$ , diastereotopic protons), 4.96 (s, 1H, CH), 5.58 (s br., 1H, NH), 6.78 (d,  $J = 8.6$  Hz, 2H, aromatic CH), 7.23 (d, 2H,  $J = 8.6$  Hz, aromatic CH).

**Diethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4g):**

M.p.: 230-232 °C (lit. [25] 228-231 °C); FT-IR ( $\nu$ ,  $\text{cm}^{-1}$  KBr disc): 3417, 3343, 3067, 2985, 1687, 1651, 1489, 1454, 1372, 1245, 1211, 1143, 1091, 883;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.14 (t,  $J = 7.1$  Hz, 6H, 2 $\text{CH}_3$ ), 2.25 (s, 6H, 2 $\text{CH}_3$ ), 3.90-4.06 (m, 4H, 2 $\text{CH}_2$ , diastereotopic protons), 4.75 (s, 1H, CH), 6.58 (d,  $J = 8.4$  Hz, 2H, aromatic CH), 6.93 (d,  $J = 8.4$  Hz, 2H, aromatic CH), 8.73 (s br., 1H, NH or OH), 9.10 (s br., 1H, NH or OH).

**Diethyl 4-(4-bromophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4h):**

M.p.: 164-166 °C (lit. [30] 162-164 °C); FT-IR ( $\nu$ ,  $\text{cm}^{-1}$  KBr disc): 3360, 3092, 2987, 1693, 1650, 1486, 1370, 1334, 1212, 1169, 1117, 1012, 843;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.25 (t,  $J = 7.1$  Hz, 6H, 2 $\text{CH}_3$ ), 2.36 (s, 6H, 2 $\text{CH}_3$ ), 4.05-4.18 (m, 4H, 2 $\text{CH}_2$ , diastereotopic protons), 4.98 (s, 1H, CH), 5.61 (s br., 1H, NH), 7.19 (d,  $J = 8.4$  Hz, 2H, aromatic CH), 7.35 (d,  $J = 8.4$  Hz, 2H, aromatic CH).

**Diethyl 4-(3-bromophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4i):**

M.p.: 163-165 °C (lit. [43] 162-164 °C); FT-IR ( $\nu$ ,  $\text{cm}^{-1}$  KBr disc): 3324, 3083, 2980, 1702, 1650, 1487, 1370, 1334, 1215, 1098, 1054, 1023, 855;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.25 (t,  $J = 7.1$  Hz, 6H, 2 $\text{CH}_3$ ), 2.36 (s, 6H, 2 $\text{CH}_3$ ), 4.04-4.20 (m, 4H, 2 $\text{CH}_2$ , diastereotopic protons), 4.98 (s, 1H, CH), 5.71 (s br., 1H, NH), 7.10 (t,  $J = 7.8$  Hz, 1H, aromatic CH), 7.22-7.28 (m, 2H, aromatic CH), 7.42 (t,  $J = 1.8$  Hz, 1H, aromatic CH).



**Diethyl 4-(4-fluorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4j):**

M.p.: 148-150 °C (lit. [27] 147-149 °C); FT-IR ( $\nu$ ,  $\text{cm}^{-1}$  KBr disc): 3343, 3067, 2985, 1687, 1652, 1489, 1334, 1211, 1123, 1091, 866;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.24 (t,  $J = 7.2$  Hz, 6H, 2 $\text{CH}_3$ ), 2.36 (s, 6H, 2 $\text{CH}_3$ ), 4.05-4.20 (m, 4H, 2 $\text{CH}_2$ , diastereotopic protons), 4.99 (s, 1H, CH), 5.68 (s br., 1H, NH), 6.91 (t,  $J = 8.4$  Hz, 2H, aromatic CH), 7.26 (dd,  $J = 8.2, 6.0$  Hz, 2H, aromatic CH).

**Diethyl 2,6-dimethyl-4-(thiophen-2-yl)-1,4-dihydropyridine-3,5-dicarboxylate (4k):**

M.p.: 173-175 °C (lit. [30] 172-174 °C); FT-IR ( $\nu$ ,  $\text{cm}^{-1}$  KBr disc): 3344, 3110, 2979, 1692, 1655, 1486, 1369, 1329, 1210, 1129, 1093, 853;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.30 (t,  $J = 7.1$  Hz, 6H, 2 $\text{CH}_3$ ), 2.36 (s, 6H, 2 $\text{CH}_3$ ), 4.17-4.27 (m, 4H, 2 $\text{CH}_2$ , diastereotopic protons), 5.37 (s, 1H, CH), 5.95 (s br., 1H, NH), 6.82 (dt,  $J = 3.2, 0.8$  Hz, 1H, arom-H), 6.87 (dd,  $J = 5.2, 3.6$  Hz, 1H, aromatic CH), 7.08 (dd,  $J = 5.0, 1.2$  Hz, 1H, aromatic CH).

**Diethyl 4-ethyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4l):**

M.p.: 110-112 °C (lit. [44] 110-112 °C); FT-IR ( $\nu$ ,  $\text{cm}^{-1}$  KBr disc): 3316, 2968, 1699, 1652, 1499, 1369, 1303, 1134, 1073, 882;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.78 (t,  $J = 7.4$  Hz, 3H,  $\text{CH}_3$ ), 1.32 (t,  $J = 7.0$  Hz, 6H, 2 $\text{CH}_3$ ), 1.35-1.41 (m, 2H,  $\text{CH}_2$ ), 2.32 (s, 6H, 2 $\text{CH}_3$ ), 3.94 (t,  $J = 5.2$  Hz, 1H, CH), 4.12-4.29 (m, 4H, 2 $\text{CH}_2$ , diastereotopic protons), 5.48 (s br., 1H, NH).

**Diethyl 2,6-dimethyl-4-propyl-1,4-dihydropyridine-3,5-dicarboxylate (4m):**

M.p.: 111-113 °C (lit. [44] 110-112 °C); FT-IR ( $\nu$ ,  $\text{cm}^{-1}$  KBr disc): 3351, 2956, 1699, 1645, 1491, 1300, 1211, 1160, 1082, 794;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ,  $\delta$ ppm): 0.86 (t, 3H,  $J = 7.1$  Hz,  $\text{CH}_3$ ), 1.19-1.34 (m, 4H, 2 $\text{CH}_2$ ), 1.31 (t, 6H,  $J = 7.2$  Hz, 2 $\text{CH}_3$ ), 2.30 (s, 6H, 2 $\text{CH}_3$ ), 3.94 (t, 1H,  $J = 5.2$  Hz, CH), 4.12-4.29 (m, 4H, 2 $\text{CH}_2$ , diastereotopic protons), 5.65 (s br., 1H, NH).

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