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Nickel nanoparticles-catalyzed synthesis of 1,4-dihydropyridines under mild and solvent-free conditions: catalytic behaviors of nickel nanoparticles

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Abstract: A novel one-pot, four-component synthesis of C_5-unsubstitiuted 1,4-dihydropyridines via unsymmetrical Hantzsch reaction using nanosized Nickel as a heterogeneous catalyst under mild reaction conditions, is described. The nickel nanoparticles, spherical in shape, have been successfully synthesized by the chemical reduction of nickel chloride with hydrazine at room temperature without any protective agent and inert gas protection. The effect of $[Ni^{2+}]/ [N_2H_4]$ in size and morphology of catalyst was investigated. Well characterized nickel nanoparticles showed remarkable activity for synthesis of C_5-unsubstitiuted 1,4-dihydropyridines and could be recycled for three consecutive runs. The performance of this reaction under solvent free conditions with heterogeneous catalysts like Ni nanoparticles could enhance its efficiency from an economic as well as a green chemistry.

Keywords: Nickel nanoparticle, Heterogeneous, Four-component, 1,4-Dihydropyridines, Hantzsch reaction.

Introduction

In the recent years, considerable attention has been devoted to the development of uniform nanometre-sized nickel nanoparticles in multi-component reactions (MCRs) due to their unique properties and potential applications in a variety of fields including electronics [1], magnetism [2], energy technology [3], or biomedicine [4]. In comparison with the noble metals, nickel nanoparticles have been much less studied in catalysis, although they have found a particular application in the growth of carbon nanotubes [5] as well as in a variety of organic reactions [6]. The synthesis of nickel nanoparticles (NiNPs) in the zerovalence state is not trivial since they readily undergo oxidation, consequently affecting their catalytic performance [7]. Nickel nanoparticles are mostly synthesised by the chemical reduction of a nickel (II) salt, with the polyol process [8] and hydrazine [9] or sodium borohydride [10] reduction being the most practiced methods. In general, the presence of an additive, as protective agent, is necessary and a common feature in all these methodologies in order to prevent particle agglomeration.

1,4-dihydropyridines (1,4-DHPs) are an important class of compounds in the field of drugs and pharmaceuticals [11]. The DHP moiety is common to numerous bioactive compounds which include vasodilators, antimutagenics, antitumors, antidiabetic agents and various antihypertensive such as nifedipine, nicardipine and amlodipine [12-15]. 1,4-DHPs are generally synthesized by classical Hantzsch method, which involves cyclocondensation of an aldehyde, β-ketoesters and ammonia either in acetic acid or in refluxing ethanol for long reaction times which typically leads to low yields [16-18]. However, this method cannot be applied for the synthesis of different substituted biologically active 1,4-DHPs. Recently, several modifications for this classical method have

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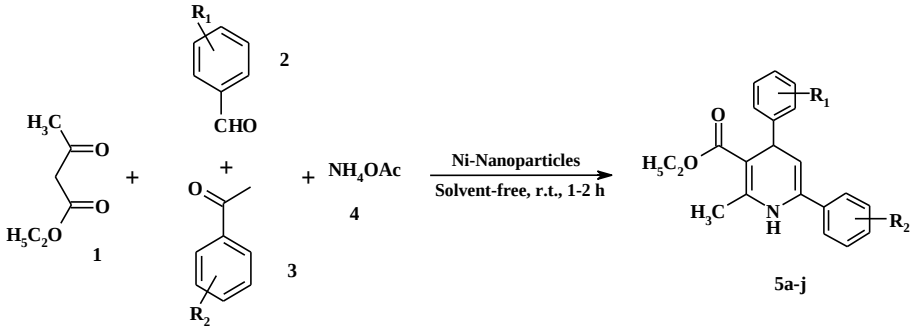
been reported for the facile and efficient synthesis of important dihydropyridine derivatives [19-24]. Other procedures comprise the use of microwaves [25], ionic liquids [26], CAN [27], tetrabutylammonium hydrogen sulfate [28], I_2 [29] and metal triflates [30]. Although most of these processes offer distinct advantages, they suffer from certain drawbacks such as longer reaction times, unsatisfactory yields, high costs, harsh reaction conditions, and the use of a large quantity of volatile organic solvents. Thus, the possibility of performing multi-component reactions under solvent free conditions with heterogeneous catalysts like Ni nanoparticles could enhance its efficiency from an economic as well as a green chemistry. Thus, the remarkable catalytic activity and easy synthesis, operational simplicity, ecofriendliness, and recoverability of the NiNPs encouraged us to utilize the NiNPs as a catalyst for the synthesis of 1,4-dihydropyridines.

To the best of our knowledge, there have been no examples of the use of Ni nanoparticles as catalysts for the four-component synthesis of C_5-unsubstitiuted 1,4-dihydropyridines in the past. Here, we would like to report the use of NiNPs for the synthesis of C_5-unsubstitiuted 1,4-dihydropyridine derivatives through a four-component reaction including ethyl acetoacetate **1**, aromatic aldehydes **2**, acetophenone derivatives **3** and ammonium acetate **4** to give compound **5a-j** in one-pot under solvent-free conditions at room temperature as shown in Scheme **1**.



Scheme 1: Synthesis of 1,4-dihydropyridines over Ni nano-particles

Results and discussion

We had the opportunity to further explore the catalytic activity of Ni-nanoparticles in the synthesis of 1,4-dihydropyridines. Herein, we wish to report on a novel synthesis of 1,4-DHP promoted by a catalytic amount of Ni-nanoparticles under solvent-free conditions at room temperature to excellent yields.

Catalytic investigation of Nickel nanoparticles:

At the onset study, to find out the suitable catalyst for the reaction, a series of experiments were performed with the standard reaction of ethyl acetoacetate **1** (1 mmol), banzaldehydes **2a** (1 mmol), acetophenone **3a** (1 mmol) and ammonium acetate **4** (1 mmol) in presence of 5 mol% each catalyst separately. The results are depicted in Table **1**. Among various catalysts including different metal salts, nickel nanoparticles were found to be the best catalyst (yield 85%, Table **1**, entry 7) for the reaction. The results are shown in Table **1**, implying the essential role of cobalt in nano-sized to carry on the reaction in reasonable time at room temperature (entries 7, 8). In presence of some nano metal oxides such as NiO, ZnO, and Fe_2O_3 the reaction the reaction proceeds in low yields toward nickel nanoparticles (Table **1**, entries 9-11).

As can be seen from Table **1**, all the traditional Lewis acid catalysts with 5 mol% loadings provided poorer yields (entries 1-6), probably due to the produce of water in condensation reaction system making the catalysts be decomposed or deactivated. As shown in Table **1** (entry 8), the model reaction preceded in a considerably lower yield under 100 °C due to sublimation of ammonium acetate in high temperature.

Effect of nickel nanoparticles concentration on synthesis of 1,4-dihydropyridines:

At the next study, to determine the appropriate concentration of the catalyst Ni nanoparticles, a mixture of ethyl acetoacetate **1** (1 mmol), banzaldehydes **2a** (1 mmol), acetophenone **3a** (1 mmol) and ammonium acetate **4** (1 mmol) was stirred at room temperature. After 6 h, only 30% of the expected product **5a** was obtained after workup and recrystallization of the crude product from ethanol (Table **2**, entry 1). To improve the yield and optimize the reaction conditions, the same reaction was carried out in the presence of a catalytic amount of 5 mol% of Ni-nanoparticles under similar conditions. Surprisingly, a significant improvement was observed and the yield of **5a** was dramatically increased to 85%

after stirring; the mixture was stirred for only 3 h (entry 2). With this optimistic result in hand, we further investigated the best reaction conditions by using different amounts of Ni-nanoparticles. An increase in the quantity of Ni-nanoparticles from 5 to 10 mol% not only decreased the reaction time from 3 h to 1.5 h, but also increased the product yield slightly from 85% to 98% (entry 3). Although the use of 15 mol% of Ni-nanoparticles permitted the reaction time to be decreased to 1 h, the yield unexpectedly decreased to 70% (entry 5).

Table 1. Synthesis of 1,4-dihydropyridines catalyzed by various catalysts[a]

Entry	Catalyst	Time (h)	Yield[b] (%)
1	$AlCl_3$	3	30
2	$Yb(OTf)_3$	3	25
3	$Hf(NPf_2)_4$	3	68
4	$SnCl_2$	3	45
5	$YbCl_3$	3	50
6	$CuSO_4$	3	Trace
7	Ni nanoparticles	3	85
8	Ni nanoparticles	3	77[c]
9	NiO nanoparticles	3	70
10	ZnO nanoparticles	3	60
11	Fe_2O_3 nanoparticles	3	75

[a] Ethyl acetoacetate/ benzaldehyde/ acetophenone/ ammonium acetate = 1:1:1:1.
[b]Isolated yields.
[C]The reaction was performed at 100 ˚C

Table 2. Optimizing the reaction conditions[a]

Entry	Ni-nanoparticles (mol%)	Time (h)	Yield (%)[b]
1	0	6.0	30
2	5	3.0	85
3	10	1.5	98
4	10[c]	6.0	40
5	15	1.0	70

[a] Ethyl acetoacetate/ benzaldehyde/ acetophenone/ ammonium acetate = 1:1:1:1.
[b] Isolated yields.
[c] Using commercial nickel powder.

A possible explanation for the low product yield is that the starting material or the final product may have been destroyed during the reaction when excess amount (15 mol%) of Ni-nanoparticles was used in the exothermic reaction and that 10 mol% Ni-nanoparticles was sufficient to catalyze the reaction effectively. In order to further expand the scope of the present method appropriately, the replacement of Ni-nanoparticles with commercial nickel powder was examined. We have carried out a reaction between ethyl acetoacetate **1**, benzaldehyde **2a**, acetophenone **3a** and ammonium acetate **4** using commercial nickel powder (10 mol%) under solvent-free conditions at room temperature.

High efficiency of nickel nano-sized than commercial powder on synthesis of 1,4-dihydropyridines:

In the process of optimization of the reaction conditions; we explored the use of different nickel powder. When the reaction was carried out by using commercial nickel powder, 40% of product **5a** was obtained in 6 h. The catalytic activity of nickel nanoparticles was evident when only 30% and 40% of the product was obtained respectively in the absence of catalyst and the use of commercial nickel powder (Table **2**, entry 1 and 4). The high efficiency of the nanoparticle is caused not only by their high surface area but also by the high concentration of low-coordinated sites and structural defects on their

surface. As the particle size is scaled down to a few nanometers, the constituting atoms have highly defective coordination environments. Most of the atoms have unsatisfied valencies and reside at the surface. Nickel nanoparticles also acts as a mild Lewis acid that catalyzes four-component, one-pot synthesis of C_5-unsubstitiuted 1,4-dihydropyridine derivatives.

Solvents effect:

We then continued to optimize the model process mentioned above by detecting the efficiency of several classic solvents chosen as the medium for comparison (Table **3**). In each case, the substrates were mixed together with 10 mol% nickel nanoparticle agitated with 3–5 ml solvent. Obviously, the polar solvents such as ethanol, acetonitrile and acetone (entries 1-3) were much better than non-polar solvents (entries 4–6). The results could be interpreted with the much better solubility of the reagents in the polar solvents. Under solvent-free conditions (entry 7), it was found that the reaction proceeded quickly but the obtained pale yellow solid contained many other by-products which were probably due to the fast self-assembling of reagents or some competitive reactions promoted by nickel nanoparticles.

Table 3. Solvent screening for the reaction between ethyl acetoacetate **1**, benzaldehyde **2a,** acetophenone **3a** and ammonium acetate[a]

Entry	Solvent	Time (h)	Yield (%)[b]
1	C_2H_5OH	6.0	60
2	CH_3CN	6.0	50
3	Acetone	6.0	30
4	Toluene	12	Trace
5	CH_2Cl_2	12	25
6	Cyclohexane	12	Trace
7	None	1.5	98

[a] All reactions were run at r.t. using Ni nanoparticles (10 mol%), ethyl acetoacetate/ benzaldehyde/ acetophenone/ ammonium acetate = 1:1:1:1.
[b] Isolated yields.

High efficiency and generality of synthesis over NiNPs

In order to extend the scope of the multicomponent reaction catalyzed by Ni nanoparticles, the conditions described above were successfully applied to various aromatic aldehydes and acetophenone derivatives with ethyl acetoacetate **1** and ammonium acetate **4** to synthesize various C_5-unsubstitiuted 1,4-dihydropyridine derivatives. As expected, satisfactory results were observed. They are summarized in Table **4**.

Table 4. Ni nanoparticles-catalyzed synthesis of C_5-unsubstitiuted 1,4-dihydropyridines

Entry	R_1	R_2	Product	Time (h)	Yield (%)[a]
1	H	H	**4a**	1.5	97
2	H	*p*-NO_2	**4b**	1.1	95
3	H	*p*-Br	**4c**	1.2	93
4	*p*-CH_3	H	**4d**	1.5	87
5	*p*-Cl	*p*-NO_2	**4e**	1.0	95
6	*m*-NO_2	*p*-Cl	**4f**	1.0	85
7	*p*-OCH_3	H	**4g**	1.5	85
8	*p*-Cl	H	**4h**	1.4	93
9	H	*p*-Cl	**4i**	1.3	90
10	*p*-NO_2	*m*-NO_2	**4j**	1.1	93

[a] Isolated yields

The results show that, generally, a wide range of aromatic aldehydes and acetophenone derivatives could react with ethyl acetoacetate and ammonium acetate smoothly and give **5a-j** in good to excellent yields (Table **4**, entries 1-10). It is also notable that the electronic property of the aromatic rings has some effects on the rate of the condensation process.

Generally speaking, shorter reaction time was needed for the substrates bearing electron-withdrawing groups on the aromatic rings (Table **3**, entries 2, 3, 5, 6, 8, 9 and 10). On the other hand, while substrates bearing electron-donating groups can afford the corresponding products with almost equally satisfactory yields, a little bit longer reaction time was necessary to complete the reaction (Table **4**, entries 1, 4, 7).

We have examined the recovery and the reuse of the catalyst. The catalyst was recovered by a simple work-up using the magnet and reused during three consecutive runs. The recovered catalyst can be reused at least three additional times in subsequent reactions without significant loss in product yield (Table **5**). In addition the separation of NiNPs was easily performed by a small magnet. Using this method, the centrifugation and complex separation processes and use of hazardous solvents is not required. In the other hand the high reusability of this catalyst and no moisture sensitivity in other predominance of this catalyst.

Table 5. The effect of reusability of Ni nanoparticles catalyst on the product **4a** yield[a]

Entry	Cycle	Yield (%)[b]
1	0	98
2	1	96
3	2	97
4	3	96

[a] *Reaction conditions:* ethyl acetoacetate (1 mmol), benzaldehyde (1 mmol) acetophenone
(1 mmol) and ammonium acetate (1 mmol), Ni nanoparticles (10 mol%), r.t.
[b] Isolated yields.

Effect of concentration of $NiCl_2$ and N_2H_4 in structures and morphologies of prepared Ni NPs:

The effects of nickel chloride concentration on the formation of nickel powders were investigated. The reduction reactions were carried out with the molar ratio of Ni^{2+}/N_2H_4= 1:3, while the Ni^{2+}concentrations varied from 0.05 M, 0.11 M to 0.33 M at 70 ^oC for 1h. Fig. **1** shows the SEM micrographs of the nickel nanoparticles obtained from different initial concentrations of Ni^{2+}. For sample a, the nanoparticles are spherical and polydispersed with diameters ranging from 100 nm to 200 nm; the sample prepared from [Ni^{2+}] = 0.11 M is monodispersed with an average size of 50 nm; Ni^{2+} concentration was too high ([Ni^{2+}] = 0.33 M), the nonspherical in shape and hard aggregated powders with broad size distribution are observed in Fig. **1**(c). The corresponding X-ray diffraction spectrum is shown in Fig. **2**. In all the samples obtained from different Ni^{2+} concentrations, only three characteristic peaks of fcc nickel (2θ = 44.5 , 51.8 and 76.4), corresponding to Miller indices (1 1 1), (2 0 0) and (2 2 2), respectively, appeared in the spectrum which indicates that all these products are pure face-centered cubic (fcc) structure metallic nickel without any other impurity. Even so, the peak intensity is different; they are typical size-dependent XRD patterns of nickel nanoparticles. The difference between particle morphology and size distribute.

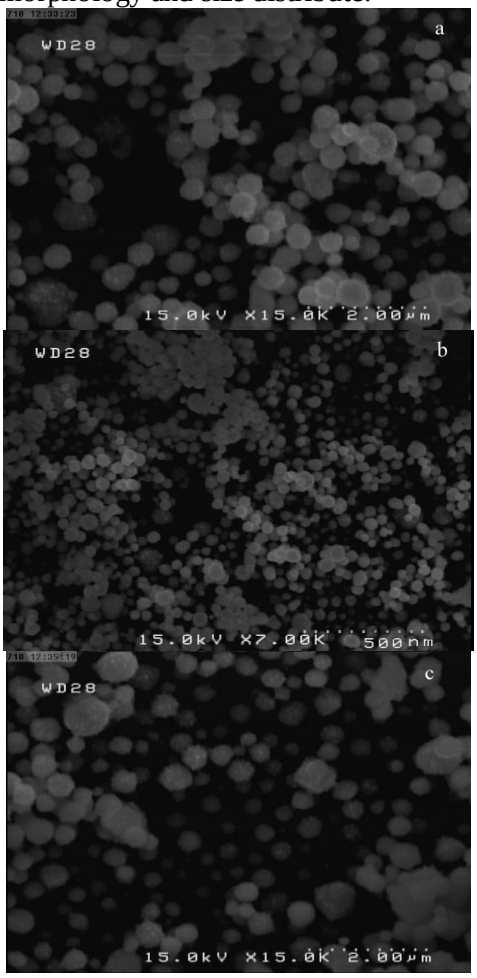


Figure 1. SEM of obtained powder from various Ni^{2+} concentrations. Ni^{2+}/N_2H_4 molar ratio is 1:3. [Ni^{2+}]= 0.05 M (a), 0.11 M (b) and 0.33 M (c).

The XRD pattern of the recovered catalyst (3rd cycle) (Fig. **3**) indicate that the structure and morphology of the catalyst remains the same after recycling. No impurities such as nickel oxide or precursor compounds were detected. Accordingly, the sample for XRD was obtained by recovering the nickel nanoparticle from the solution using the centrifugation method, and finally the obtained precipitate was dried

and washed by ethanol. Three characteristic peaks (2θ = 44.5, 51.8, and 76.4) marked by their indices (111), (200), and (222) corresponding Ni were observed. A single-phase face-centered cubic (FCC) structure and the size were calculated from the full width at the half maximum (FWHM) of the strongest peak (111) by using the Scherer formula. The size of the calculated particles is comparable with the corresponding size from SEM analysis.

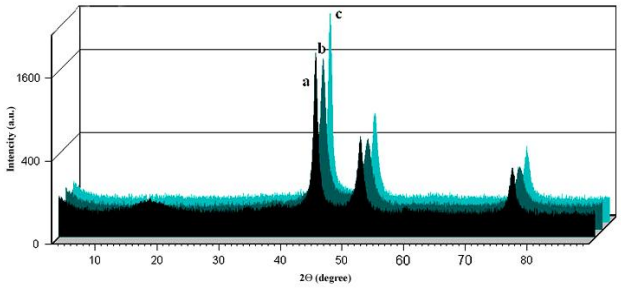


Figure 2. XRD of obtained powder from various Ni^{2+} concentrations. Ni^{2+}/N_2H_4 molar ratio is 1:5. $[Ni^{2+}]$= 0.05 M (a), 0.11 M (b) and 0.33 M (c).

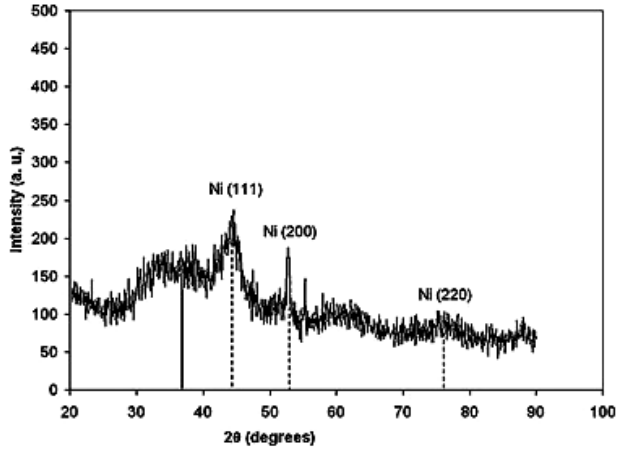


Figure 3. X-ray diffraction spectrum of recovered Ni nanoparticles using Cu-Kα (1.54 Å).

Conclusion

In summary, a synthetic rout without any other protective agent and inert atmosphere protection has been successfully developed for the preparation of spherical metallic nickel nanoparticles by hydrazine reduction. The form of nanoparticles is a potential alternative to the use of noble-metal-based catalysts for Hantzsch condensation. This paper provides very simple and efficient solvent-free method for the synthesis of 1,4-dihydropyridines via Hantzsch condensation using Ni nanoparticles as a catalyst. This catalyst is expected to contribute to the development of more environment-benign methods and forms as a part of nanometal chemistry. The mildness of the conversion, experimental simplicity, compatibility with various functional groups, excellent yields, shorter reaction time, and the easy work-up makes this procedure more attractive in synthesizing a variety of these derivatives.

Experimental

General:

Melting points were determined in open capillaries using an Electrothermal Mk3 apparatus and are uncorrected. Infrared (IR) spectra were recorded using a Perkin-Elmer FT-IR 550 spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded with a Bruker DRX-400 spectrometer at 400 and 100 MHz respectively. NMR spectra were obtained in $CDCl_3$ solutions. X-ray measurement was performed on a Rigaku D/max III.V X-ray diffractometer using Cu-Kα radiation (k = 0.154 nm). The particle size was determined by a SEM image using JEOL Model JEM-200 EX at 80 kV. The element analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer carried out on Perkin-Elmer 240c analyzer.

Typical experimental procedure for the preparation of catalyst:

In this work, the micro emulsion solutions were prepared by solubilizing an aqueous nickel chloride ($NiCl_2$, 0.05 M), hydrazine (N_2H_4, 1.0 M) solution into double distilled water (22 ml), cetyltrimethyl ammonium bromide (CTAB, 0.025 M), and *n*-hexanol (45 ml) mixture. The pH of aqueous 1 M N_2H_4 solution was adjusted to 13 by adding an ammonia solution with continuous stirring. The reaction mixture was refluxed at 70 ºC for one hour till the final color of the solution became black. The growth of Ni nanoparticles was completed after 1 h. The particle size and structure of the resultant Ni nanoparticles have been characterized by X-ray diffraction (XRD), Scanning electron microscopy (SEM).

General procedure for the synthesis of 2-methyl-4,6-diphenyl-1,4-dihydro-3-pyridinecarboxilate derivatives

A mixture of ethyl acetoacetate (1 mmol), aromatic aldehydes (1mmol), acetophenone derivatives (1 mmol) ammonium acetate (1 mmol) and Ni nanoparticle (10 mol%) was stirred under solvent-free conditions at room temperature for an appropriate time, as shown in Table **3**. After completion of the reaction

(TLC monitoring), it was extracted with ethyl acetate; the organic layer was dried over sodium sulphate and concentrated in a vacuum to afford the crude products. The pure products were obtained by recrystallization from ethanol. Nanoparticles were recovered by centrifuging the aqueous layer and reutilized three times for the same reaction (Table **4**).

*Ethyl 2-methyl-4,6-diphenyl-1,4-dihydro-3-pyridinecarboxilate (**4a**):*

Pale yellow solid, mp 245-247 °C, 0.31 g, yield: 97%. [Found: C, 78.79; H, 6.60; N, 4.35. $C_{21}H_{21}NO_2$ requires: C, 78.97; H, 6.63; N, 4.39%.] R_f (30% EtOAc/*n*-Hexane): 0.65; ν_{max} (KBr, neat) 3341, 1688, 1726 cm^{-1}; δ_H (400 MHz $CDC1_3$) 1.09 (3H, t, *J* 7.2Hz, MeCH$_2$O), 2.23 (3H, s, C=CMe), 3.91 (2H, q, *J* 7.2 Hz, MeCH$_2$O), 5.25 (1H d, *J* 5.7Hz, C=CH), 5.94 (1H, d, *J* 5.7Hz, CH), 6.57 (1H, s, NH), 7.0-7.50 (m, 5H, Ar), 7.60-8.0 (m, 5H); δ_C (100 MHz, $CDCl_3$) 14.2, 18.2, 38.4, 61.2, 102.1, 105.7, 123.8, 126.7, 127.6, 128.37, 128.7, 129.8, 134.5, 140.9, 143.9, 147.2, 171.3.

*Ethyl 2-methyl-6-(4-nitrophenyl)-4-phenyl-1,4-dihydro-3-pyridinecarboxilate (**4b**):*

Pale yellow solid, mp 232-235 °C, 0.34 g, yield: 95%. [Found: C, 69.15; H, 5.49; N, 7.67. $C_{21}H_{20}N_2O_4$ requires: C, 69.22; H, 5.53; N, 7.69%.] R_f (30% EtOAc/*n*-Hexane): 0.57; ν_{max} (KBr, neat) 3342, 1687, 1728, 1436, 1354 cm^{-1}; δ_H (400 MHz $CDC1_3$) 1.18 (3H, t, *J* 7.1Hz, MeCH$_2$O), 2.19 (3H, s, C=CMe), 3.56 (2H, q, *J* 7.1Hz, MeCH$_2$O), 5.42 (1H, d, *J* 6.1Hz, C=CH), 6.23 (1H, d, *J* 6.1Hz, CH), 6.65 (1H, s, NH), 7.0-7.40 (5H, m, Ar), 7.52 (2H, d, *J* 8.1Hz, C=CH), 7.87 (2H, d, *J* 8.1Hz, C=CH); δ_C (100 MHz, $CDCl_3$) 14.2, 18.2, 37.9, 61.1, 103.7, 105.8, 122.8, 124.7, 128.3, 130.3, 131.4, 141.4, 142.5, 143.9, 147.5, 148.1, 169.6.

*Ethyl 6-(4-bromophenyl)-2-methyl-4-phenyl-1,4-dihydro-3-pyridinecarboxilate (**4c**):*

Pale yellow solid, mp 257-259 °C, 0.37 g, yield: 93%. [Found: C, 63.25; H, 5.03; N, 3.51. $C_{21}H_{20}BrNO_2$ requires: C, 63.33; H, 5.06; N, 3.52%.] R_f (30% EtOAc/*n*-Hexane): 0.67; ν_{max} (KBr, neat) 3344, 1679, 1731 cm^{-1}; δ_H (400 MHz $CDC1_3$) 1.16 (3H, t, *J* 6.9Hz, MeCH$_2$O), 2.17 (3H, s, C=CMe), 3.78 (2H, q, *J* 6.9Hz, MeCH$_2$O), 5.70 (1H, d, *J* 6.7Hz, C=CH), 6.64 (1H, d, *J* 6.7Hz, CH), 6.89 (1H, s, NH), 7.0-7.25 (5H, m, Ar), 7.36 (2H, d, *J* 7.9Hz, C=CH), 7.45 (2H, d, *J* 7.9Hz, C=CH); δ_C (100 MHz, $CDCl_3$) 14.2, 18.2, 35.7, 60.9, 104.1, 106.1, 120.8, 123.9, 127.5, 128.2, 129.7, 130.2, 134.90, 141.3, 143.7, 146.8, 169.1.

*Ethyl 2-methyl-4-(4-methylphenyl)-6-phenyl-1,4-dihydro-3-pyridinecarboxilate (**4d**):*

Pale yellow solid, mp 235-238 °C, 0.29 g, yield: 87%. [Found: C, 79.17; H, 6.92; N, 4.18. $C_{22}H_{23}NO_2$ requires: C, 79.25; H, 6.95; N, 4.20%.] R_f (30% EtOAc/*n*-Hexane): 0.73; ν_{max} (KBr, neat) 3344, 1679, 1731cm^{-1}; δ_H (400 MHz $CDC1_3$) 1.19 (3H, t, *J* 6.8Hz, MeCH$_2$O), 1.98 (3H, s, Me), 2.20 (3H, s, C=CMe), 3.87 (2H, q, *J* 6.8Hz, MeCH$_2$O), 5.73 (1H, d, *J* 7.1Hz, C=CH), 6.69 (1H, d, *J* 7.1Hz, CH), 6.79 (1H, s, NH), 7.0-7.50 (5H, m, Ar), 7.66 (2H, d, *J* 8.1Hz, C=CH), 7.98 (2H, d, *J* 8.1Hz, C=CH); δ_C (100 MHz, $CDCl_3$) 14.2, 18.2, 22.5, 35.6, 60.9, 104.1, 106.2, 120.7, 123.8, 127.5, 128.1, 130.2, 130.4, 134.8, 141.2, 143.7, 146.7, 170.1.

*Ethyl 4-(4-chlorophenyl)-2-methyl-6-(4-nitrophenyl)-1,4-dihydro-3-pyridinecarboxilate (**4e**):*

Pale yellow solid, mp 211-213 °C, 0.39 g, yield: 96%. [Found: C, 63.14; H, 4.78; N, 7.01. $C_{21}H_{19}ClN_2O_4$ requires: C, 63.24; H, 4.80; N, 7.02%.] R_f (30% EtOAc/*n*-Hexane): 0.63; ν_{max} (KBr, neat) 3347, 1674, 1736 Cm^{-1}; δ_H (400 MHz $CDC1_3$) 1.19 (3H, t, *J* 6.8Hz, MeCH$_2$O), 2.14 (3H, s, C=CMe), 3.87 (2H, q, *J* 6.8Hz, MeCH$_2$O), 5.74 (1H, d, *J* 6.6Hz, C=CH), 6.62 (1H, d, *J* 6.6Hz, CH), 7.12 (1H, s, NH), 7.19 (2H, d, *J* 7.8Hz, C=CH), 7.26 (2H, d, *J* 7.8Hz, C=CH), 7.45 (2H, d, *J* 7.9Hz, C=CH), 7.65 (2H, d, *J* 7.9Hz, C=CH); δ_C (100 MHz, $CDCl_3$) 14.1, 19.1, 33.3, 61.4, 103.7, 105.8, 124.8, 128.1, 128.9, 131.6, 132.6, 140.9, 141.2, 141.3, 146.3, 147.6, 167.8.

*Ethyl 6-(4-chlorophenyl)-2-methyl-4-(3-nitrophenyl)-1,4-dihydro-3-pyridinecarboxilate (**4f**):*

Pale yellow solid, mp 218-220 °C, 0.33 g, yield: 85%. [Found: C, 63.14; H, 4.78; N, 7.01. $C_{21}H_{19}ClN_2O_4$ requires: C, 63.24; H, 4.80; N, 7.02%.] R_f (30% EtO EtOAc/*n*-Hexane): 0.70; ν_{max} (KBr, neat) 3344, 1675, 1721 Cm^{-1}; δ_H (400 MHz $CDC1_3$) 1.16 (3H, t, *J* 7.1Hz, MeCH$_2$O), 2.11 (3H, s, C=CMe), 3.82 (2H, q, *J* 7.1Hz, MeCH$_2$O), 5.62 (1H, d, *J* 6.9Hz, C=CH), 6.32 (1H, d, *J* 6.9Hz, CH), 7.25 (1H, s, NH), 7.34 (2H, d, *J* 7.3Hz, C=CH), 7.43 (2H, d, *J* 7.3Hz, C=CH), 7.48 (1H, dd, *J* 8.1Hz, *J* 7.8Hz, C=CH), 7.53 (1H, d, *J* 7.8Hz, C=CH), 8.13 (1H, dd, *J* 8.1Hz, *J* 2Hz, C=CH), 8.32 (1H, d, *J* 2Hz, C=CH); δ_C (100 MHz, $CDCl_3$) 14.1, 20.2, 33.9, 61.1, 104.2, 105.8, 122.4, 123.4, 124.9, 127.7, 132.5, 133.3, 134.4, 136.2, 140.1, 141.3, 143.5, 149.6, 168.3.

*Ethyl 4-(4-methoxyphenyl)-2-methyl-6-phenyl-1,4-dihydro-3-pyridinecarboxilate (**4g**):*

Pale yellow solid, mp 223-225 °C, 0.29 g, yield: 85%. [Found: C, 75.58; H, 6.60; N, 4.00. $C_{22}H_{23}NO_3$ requires: C, 75.62; H, 6.63; N, 4.01%.] R_f (30% EtOAc/*n*-Hexane): 0.56; ν_{max} 3342, 1679, 1729 Cm^{-1}; δ_H (400 MHz $CDC1_3$) 1.19 (3H, t, *J* 6.9Hz, MeCH_2O), 2.20 (3H, s, C=CMe), 3.53 (3H, s, OMe), 3.77 (2H, q, *J* 6.9Hz, MeCH_2O), 6.04 (1H, d, *J* 7.4Hz, C=CH), 6.54 (1H, d, *J* 7.4Hz, CH), 6.88 (1H, s, NH), 6.99 (2H, d, *J* 7.7Hz, C=CH), 7.10-7.30 (5H, m, Ar), 7.56 (2H, d, *J* 7.7Hz, C=CH); δ_C (100 MHz, $CDCl_3$) 14.1, 17.9, 36.3, 55.4, 62.3, 98.2, 106.3, 113.6, 126.4, 127.2, 128.5, 130.2, 134.5, 139.6, 140.4, 141.7, 155.8, 169.8.

*Ethyl 4-(4-chlorophenyl)-2-methyl-6-phenyl-1,4-dihydro-3-pyridinecarboxilate (**4h**):*

Pale yellow solid, mp 252-255 °C, 0.32 g, yield: 92%. [Found: C, 71.20; H, 5.65; N, 3.93 $C_{21}H_{20}ClNO_2$ requires: C, 71.28; H, 5.70; N, 3.96%.] Rf (30% EtOAc/*n*-Hexane): 0.55; ν_{max} (KBr, neat) 3346, 1673, 1722 Cm^{-1}; δ_H (400 MHz $CDC1_3$) 1.17 (3H, t, *J* 6.8Hz, MeCH_2O), 2.14 (3H, s, C=CMe), 3.52 (2H, q, *J* 6.8Hz, MeCH_2O), 6.37 (1H, d, *J* 7.1Hz, C=CH), 6.98 (1H, d, *J* 7.1Hz, CH), 7.21 (1H, s, NH), 7.32 (2H, d, *J* 7.2Hz, C=CH), 7.30-7.50 (5H, m, Ar), 7.71 (2H, d, *J* 7.2Hz, C=CH); δ_C (100 MHz, $CDCl_3$) 14.3, 18.7, 36.9, 63.1, 99.3, 107.8, 125.4, 127.7, 128.3, 129.3, 130.2, 132.7, 134.5, 139.6, 141.3, 141.7, 170.1.

*Ethyl 6-(4-chlorophenyl)-2-methyl-4-phenyl-1,4-dihydro-3-pyridinecarboxilate (**4i**):*

Pale yellow solid, mp 264-266 °C, 0.31 g, yield: 90%. [Found: C, 71.20; H, 5.65; N, 3.93 $C_{21}H_{20}ClNO_2$ requires: C, 71.28; H, 5.70; N, 3.96%.] Rf (30% EtOAc/n-Hexane): 0.60; ν_{max} (KBr, neat) 3348, 1669, 1745 Cm^{-1}; δ_H (400 MHz $CDC1_3$) 1.22 (3H, t, *J* 7.4Hz, MeCH_2O), 2.11 (3H, s, C=CMe), 3.44 (2H, q, *J* 7.4Hz, MeCH_2O), 6.76 (1H, d, *J* 6.1Hz, C=CH), 7.10 (1H, d, *J* 6.1Hz, CH), 7.29 (1H, s, NH), 7.0-7.3 (5H, m, Ar), 7.34 (2H, d, *J* 7.4Hz, C=CH), 7.55 (2H, d, *J* 7.4Hz, C=CH); δ_C (100 MHz, $CDCl_3$) 14.5, 19.1, 36.1, 62.3, 100.1, 106.9, 122.3, 124.2, 127.2, 130.2, 130.9, 132.2, 133.5, 140.6, 141.4, 143.2, 170.3.

*Ethyl 2-methyl-6-(3-nitrophenyl)-4-(4-nitrophenyl)-1,4-dihydro-3-pyridinecarboxilate (**4j**):*

Pale yellow solid, mp 203-205 °C, 0.37 g, yield: 92%. [Found: C, 60.65; H, 4.26; N, 10.59. $C_{21}H_{19}lN_3O_6$ requires: C, 60.76; H, 4.33; N, 10.63%.] R_f (30% EtOAc/*n*-Hexane): 0.82; ν_{max} (KBr, neat) 3347, 1671, 1712 Cm^{-1}; δ_H (400 MHz $CDC1_3$) 1.17 (3H, t, *J* 6.9Hz, MeCH_2O), 2.15 (3H, s, C=CMe), 3.65 (2H, q, *J* 6.9Hz, MeCH_2O), 5.80 (1H, d, *J* 7.4Hz, C=CH), 6.64 (1H, d, *J* 7.4Hz, CH), 7.15 (1H, s, NH), 7.44 (1H, d, *J* 7.7Hz, C=CH), 7.53 (1H, s, C=CH), 7.89 (1H, dd, *J* 8.2Hz, *J* 7.7Hz, C=CH), 8.12 (2H, d, *J* 7.2Hz, C=CH), 8.34 (2H, d, *J* 7.2Hz, C=CH); 8,57 (1H, d, J=8.2Hz, C=CH); δ_C (100 MHz, $CDCl_3$) 14.1, 21.1, 32.3, 60.5, 100.3, 105.8, 119.4, 122.4, 126.5, 129.4, 130.6, 133.3, 135.6, 140.5, 143.7, 144.5, 145.8, 148.5, 169.5.

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