Ultrasound-promoted green synthesis of 1,4-dihydropyridines using fuctionalized MWCNTs as a highly efficient heterogeneous catalyst

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ABSTRACT
A new method for multi-component synthesis of 1,4-dihydropyridine derivatives (1,4-DHPs) in the presence of meglumine supported on multiwalled carbon nanotubes (MWCNTs@meglumine) as a new heterogeneous, highly efficient and reusable catalyst was investigated. The reaction was performed under ultrasonic irradiation in EtOH at room temperature. A new, highly efficient heterogeneous catalyst, short reaction times, high to excellent yield of products, and safe and clean conditions are the advantages of the presented method.

1. Introduction
1,4-Dihydropyridines (1,4-DHPs) as an important class of organic compounds have attracted growing interest from both organic and medicinal chemists owing to their diverse range of biological and pharmacological activities such as antihypertensive and calcium channels blocker (1–7). Furthermore, these compounds have some medicinal utility such as neuroprotectant, cerebral anti-ischemic activity in the treatment of Alzheimer’s disease, platelet anti-aggregatory activity and chemosensitizer behavior in tumor therapy (8). These examples clearly indicate the remarkable potential of dihydropyridine derivatives as sources of valuable drugs.

1,4-DHPs are generally synthesized using the classical Hantzsch method, through cyclocondensation of an aldehyde, β-ketoesters and ammonia either in acetic acid or in refluxing ethanol for long reaction times. This method typically leads to low yields (9, 10).

In comparison with the classical methods for synthesis of complex molecules by sequential synthesis, multi-component reactions (MCRs) allow the assembly of complex molecules in one-pot and show a facile execution, high atom-economy and high selective conditions (11–14). As a one-pot reaction, MCRs generally afford good yields and are fundamentally different from two-component and stepwise reactions.

Several modifications of this classical method have been reported for the facile and efficient synthesis of 1,4 DHP derivatives (15–20). Various catalysts were used for the synthesis of these compounds such as ionic liquid (21), tetrabutylammonium hydrogen sulfate (22), I₂ (23), cellulose sulfuric acid (24), HY-Zeolite (25), nano-Fe₂O₃ (26) nano-Fe₂O₃ (27), SnCl₄-functionalized nano-Fe₃O₄ encapsulated-silica particles (28), ZnFe₂O₄ nanopowder (29), 3D printed α-Al₂O₃ (30), Alginic Acid (31), Fe₃O₄@SiO₂ (32), magnetic nanoparticle supported Ni²⁺-containing ionic liquid (33) and metal triflate (34).

Recently, the direction of science and technology has been shifted towards eco-friendly and natural product resources (such as natural biopolymers) that are attractive candidates in the search for solid support catalysts (24, 35–46). Also in recent years, ultrasound has been used to accelerate the chemical reactions proceed via the
formation and collapse of transient cavitation bubbles. The ultrasonic effect induces very high local pressure and temperatures inside the bubbles and enhances the mass transfer and turbulent flow in the liquid (7, 47–50).

Carbon nanotubes (CNTs) with exceptional physical properties such as high specific surface area, excellent electron conductivity incorporated with the good chemical inertness and relatively high oxidation stability is a promising support material for a heterogeneous catalyst (35, 36, 51, 52). In view of recent surge in the use of heterogeneous catalysts, we wish to report a simple, convenient and efficient method for the preparation of 1,4-DHPs in the presence of multiwalled carbon nanotubes (MWCNTs@meglumine), as a heterogeneous inexpensive, highly efficient and reusable catalyst under ultrasonic irradiation (Scheme 1). In fact, the synthesized CNT-based catalyst permitted us to use a solid, mild and reusable catalyst instead of meglumine (alone) as a highly soluble and homogeneous catalyst.

2. Results and discussion

In the present work, we wish to report a new synthetic method for preparation of 1,4-dihydropyridine derivatives in the presence of MWCNTs@meglumine as a new high efficient and reusable catalyst. The catalyst was prepared through a three-step process. Firstly, raw MWCNTs were oxidized and then, the generated carboxylic groups were converted to –COCl using SOCl₂. Finally, the reaction of MWCNTs-COCI with meglumine, lead to formation of MWCNTs@meglumine through the nucleophilic substitution reaction between –OH or –NHMe groups of meglumine and acyl chloride groups on CNT surfaces (Scheme 2). In fact, this process is a method for immobilization of meglumine as a highly soluble catalyst on CNT surfaces, for preparing an effective heterogeneous and reusable catalyst, in following of green chemistry protocol.

Fourier transform infrared (FTIR), SEM, Energy-dispersive X-ray spectroscopy (EDX), TGA, Raman and elemental analysis (CHN) were used for characterization and confirmation of the structure of synthetic heterogeneous catalyst. Figure 1(a) show the FTIR of raw CNTs. Since pristine nanotubes are completely symmetric in structure, vibrations cannot change the dipolar moments and consequently, sharp peaks do not generate such organic compounds. A weak absorption band related to stretching vibration of C=O is located at 1642 cm⁻¹. The broad peak at about 3393 cm⁻¹ is attributed to the presence of O-H groups on the surfaces of the as-received CNTs, and is believed to result from either ambient atmospheric moisture tightly bound to the CNTs or related to the absorption of water by potassium bromide.

In the FTIR spectrum of the oxidized MWCNT (Figure 1 (b)), the stretching absorption peaks of C=O and O–H for the carboxylic groups (COOH) can be clearly observed at 1715 and 3403 cm⁻¹. The stretching absorption peaks of aliphatic C–H, C=C, and C=O bonds appeared at 2854 and 2924, 1636 and 1400 and 1112 cm⁻¹, respectively.

Figure 1(c) shows the FTIR of MWCNT-COCI. As can be seen, the peak at 1722 cm⁻¹ is due to the C=O stretching vibration of the COCl group, and the peak at about
570 cm\(^{-1}\) can be assigned to the stretching of the C-Cl groups attached on the nanotube surfaces. Also, the main peaks from C=C, C-H and C-O bands can be observed at 2854, 2923, 1633, 1400 and 1118 cm\(^{-1}\), respectively.

In FTIR of Meglumine (Figure 2(a)), the stretching vibration peaks of C=O and C=N, can be clearly observed at 1076 and 1238 cm\(^{-1}\) also aliphatic C-H appeared at 2854 and 2915 cm\(^{-1}\), respectively. The broad peaks at 3249 and 3331 cm\(^{-1}\) were attributed to NH and OH stretching modes. Comparison between the FTIR of meglumine and MWCNTs@meglumine (Figure 2(a,b)) indicate that the main peaks in meglumine structure were appeared in catalyst and the attachment of meglumine on CNT surfaces was occurred successfully.

TGA analysis was used for determining the percentage of functionalization of MWCNTs (Figure 2). TGA measurement was performed in air at a rate of 5°C/min (from 50°C to 650°C). As shown in Figure 3, the raw CNTs show only about 3% weight loss between 150°C and 650°C, but in the case of MWCNTs@meglumine, 13% of weight loss was observed between 150°C and 450°C (the range of temperature that organic groups attached on CNT surfaces, were decomposed). It can be concluded that the modification of CNTs performed truly.

X-ray diffraction (XRD) provided useful information about structural properties of CNT-based materials. Figure 4 shows the XRD patterns of raw MWCNTs and MWCNTs@meglumine. The sharpest diffraction peak at around 2\(\theta\) = 26.3° corresponded to 002 planes of graphite (53). Also, the similarity of XRD patterns of raw and treated MWCNTs, meaning that chemical attachment of meglumine, only affected the CNT surfaces without any destruction of the CNT original structure (54–56).

The morphology of raw and functionalize CNTs was investigated using SEM images (Figure 5). As can be seen in these images, any changes and damages have not been occurred on the length and structure of MWCNTs and functionalization process only affected the surfaces of this nanostructure.

EDX was applied for elemental analysis of the MWCNTs@meglumine structure. The EDX spectrum presented in Figure 6 confirmed the presence of N, O and C elements in the prepared catalyst. This result is in agreement to elemental analysis, FTIR and Raman spectroscopy techniques.

Raman spectroscopy was used as a powerful technique for the characterization of raw and functionalized CNTs structures. As shown in Figure 7, two main peaks existed at 1337 cm\(^{-1}\) (as D-band) and 1574 cm\(^{-1}\) (as G band) both in raw and treated MWCNTs (57, 58). The D-band is related to the amorphous or disordered carbon nanostructures, vacancies and also defects on the
nanotube walls and the G band originates from in-plane tangential stretching of C==C bonds on graphene sheets with sp² hybridized carbons. Chemical attachment of functional groups on CNTs surfaces converted the hybridization of carbons from sp² towards greater sp³ character and hence contributes to increase in the intensity of the D-band (I_D). The I_D/I_G ratio can be calculated for both raw and treated MWCNTs. The I_D/I_G ratio for pristine MWCNTs was 0.89 in contrast, the I_D/I_G of MWCNTs@meglumine was increased to 1.24. This result demonstrated the chemical attachment of meglumine to the CNT surfaces.

In continuation, elemental analysis was used as a powerful characterization method for confirmation of the catalyst composition. The percentage of C, H, N and O in catalyst was 89.6, 2.2, 0.99 and 5.9, respectively, in comparison with raw CNTs contents (97.9, 0.61, 0.07 and 0.68). Obtained results demonstrated that meglumine was chemically attached on MWCNT surfaces.

After the preparation and characterization of supported catalyst, optimization of solvent and catalyst amounts was investigated for the synthesis of 1,4-DHPs in the presence of the prepared catalyst. In an initial endeavor, a model reaction was mentioned using 4-nitrobenzaldehyde (1 mmol), NH₄OAc (1 mmol) and ethylacetoacetate (2 mmol). All reactions for optimization of solvent and catalyst amount were performed under a power of 60 W. As can be seen in Table 1, in the case of catalyst optimization, initially, blank reaction was done without catalyst (in EtOH) and only 20% of product was obtained after 60 min (entry 1). The same reactions were performed in the presence of further amounts of catalyst under similar conditions. When the quantity of catalyst was increased from 0.01 to 0.02 g, the time of reaction was decreased from 30 to 20 min. and the yield was raised from 73% to 90% (entry 2, 3). Also, 0.03 g of catalyst, have not increased the yield of reaction (entry 4) because of further amount of catalyst, can decompose the product to initial molecules. As a result, 0.02 g of catalyst can be considered as optimized amount in EtOH as solvent.
Solvent effect on yield and time of reaction was examined using several organic solvents. As shown in Table 2, it was found that EtOH is an efficient and superior solvent in comparison to others. From results depicted in Tables 1 and 2, it can be concluded that 0.02 g of catalyst in EtOH (as solvent) is the optimum condition for the mentioned reaction.

In continuation, power of ultrasonic irradiation was optimized. In this way, model reaction was occurred in the presence of 0.02 g of catalyst in EtOH (as solvent) is the optimum condition for the mentioned reaction.

In continuation, power of ultrasonic irradiation was optimized. In this way, model reaction was occurred in the presence of 0.02 g of catalyst. The reaction was done in EtOH as solvent and different powers were applied. Results in Table 3 indicated that the reaction in power of 70 W was afforded the best yield (95%) after 15 min. Also, higher power (75 W) has no effect on time and yield of reaction. Furthermore, in silent condition, only 25% of product was obtained after 60 min (entry 5). These results show that ultrasound irradiation as a powerful and green condition enhances the yield of reactions in short times.

After the optimization of the reaction conditions, we investigated the synthesis of 1,4-DHPs, using 1 mmol ary-laldehyde, 2 mmol ethyl acetoacetate (or 1 mmol ethyl acetoacetate and 1 mmol dimerone), 1 mmol ammonium acetate and 0.02 g of MWCNTs@megulmine as catalyst, under ultrasonic irradiation (with power of 70 W) in EtOH. As expected, satisfactory results were obtained.

From results in Table 4, it is clear that in the presence of efficient CNT-based catalyst, products were obtained in high to excellent yields and reaction times were shorter. It is also noted that the
arylaldehydes bearing electron-withdrawing groups on the aromatic rings has higher yields and shorter reaction times and substrates carrying electron donating groups afforded the corresponding products with satisfactory yields. Furthermore, in the case of 2,4-dichlorobenzaldehyde, the yield is lower than arylaldehydes bearing electron-withdrawing groups due to steric effect (entry 13).
Table 1. Optimization of catalyst amount.

| Entry | Catalyst (g) | Time (min) | Yield (%) |
|-------|--------------|------------|-----------|
| 1     | –            | 60         | 20        |
| 2     | 0.01         | 30         | 73        |
| 3     | 0.02         | 20         | 90        |
| 4     | 0.03         | 20         | 86        |

*a* Isolated yield.

Table 2. Solvent effect on the yield and time of reaction.

| Entry | Solvent | Time (min) | Yield (%) |
|-------|---------|------------|-----------|
| 1     | H2O     | 20         | 51        |
| 2     | CH3CN   | 30         | 44        |
| 3     | EtOH    | 20         | 90        |
| 4     | EtOH/H2O (2:1) | 20 | 57       |
| 5     | CHCl2   | 30         | 37        |

*a* Model reaction in the presence of 0.02 g of catalyst and power of 60 W.

Table 3. Optimization of the power of ultrasonic irradiation.

| Entry | Power (W) | Time (min) | Yield (%) |
|-------|-----------|------------|-----------|
| 1     | 60        | 20         | 90        |
| 2     | 65        | 20         | 92        |
| 3     | 70        | 15         | 95        |
| 4     | 75        | 15         | 95        |
| 5     | –         | 60         | 25*a      |

*a* Blank reaction in silent conditions.

Table 4. Synthesis of 1,4-DHPs using MWCNTs@meglumine under ultrasonic condition.

| Entry | Product | R         | Time (min) | Yield (%) | mp (°C) (found, reported) |
|-------|---------|-----------|------------|-----------|--------------------------|
| 1     | 5a      | 4-NO2     | 15         | 95        | 127–129, 130–132 (59)    |
| 2     | 5b      | 4-CH3     | 15         | 87        | 156–158, 158–160 (39)    |
| 3     | 5c      | 4-Cl      | 15         | 95        | 144–146, 144–146 (60)    |
| 4     | 5d      | 3-NO2     | 17         | 92        | 163–165, 162–164 (60)    |
| 5     | 5e      | H         | 20         | 90        | 156–158, 157–159 (60)    |
| 6     | 5f      | 2-F       | 25         | 95        | 145–147, 148–152 (61)    |
| 7     | 5g      | 4-CH3     | 30         | 85        | 141–143, 142–145 (62)    |
| 8     | 5h      | 4-Br      | 18         | 90        | 146–148, 148–150 (62)    |
| 9     | 5i      | 3-Oh      | 22         | 82        | 170–173, 172–175 (62)    |
| 10    | 5j      | 2-furyl   | 29         | 90        | 157–160, 159–161 (63)    |
| 11    | 5k      | 2-thienyl | 28         | 90        | 151–154, 153–155 (61)    |
| 12    | 5l      | 4-Oh      | 25         | 85        | 228–231, 227–228 (64)    |
| 13    | 5m      | 2,4-dichloro | 20     | 88        | 149–151, 153–155 (65)    |
| 14    | 6a      | 4-NO2     | 18         | 92        | 238–240, 241–243 (66)    |
| 15    | 6b      | 4-Cl      | 16         | 94        | 231–233, 229–231 (67)    |
| 16    | 6c      | 3-NO2     | 18         | 92        | 180–182, 181–183 (68)    |
| 17    | 6d      | 4-CH3     | 34         | 88        | 254–256, 257–258 (60)    |
| 18    | 6e      | 4-CH3     | 28         | 85        | 256–258, 257–258 (68)    |
| 19    | 6f      | H         | 23         | 88        | 212–214, 214–216 (68)    |
| 20    | 6g      | 2-thienyl | 30         | 90        | 226–228, 223–225 (69)    |

*a* Isolated yield.

2.1. Reusability of catalyst

The reusability of heterogeneous catalyst was examined by separation of catalyst from the reaction mixture, washed with EtOH/H2O and dried. Recovered catalyst was used for four additional times in subsequent reaction. As a result, synthetic catalyst has high efficiency without significant loss in product yields (95–88%) even after four times recycling (Figure 8).

The leaching behavior of catalyst was tested through the filtration method. In this way, model reaction was performed in the presence of 0.02 g of catalyst under ultrasonic irradiation (70 W) for 7:30 min (half time of reaction). Then the catalyst was separated and the reaction was continued (without catalyst) for another 7:30 min. After the separation and purification of product, the obtained yield was 42%. Consequently, there is no leaching or degradation of catalyst during the reaction process.

A plausible mechanism for the preparation of 1,4-DHPs in the presence of heterogeneous catalyst is presented in Scheme 3. As can be seen, at the first stage, MWCNTs@meglumine activated the carbonyl group of β-ketoester for preparation of 1. Also, the catalyst can be considered as a base in aldol condensation of β-ketoester and aryl aldehyde to produce 2. In next step, Michael addition between 1 and 2, and then cyclization of 4 with removal the H2O lead to product (6).

Furthermore, a comparison between literature reports (in classical heating) and presented method was investigated. According to the results in Table 5, it is clear that MWCNTs@meglumine as an efficient catalyst is comparable to other applied catalysts in terms of time and yield of products. Furthermore, in most cases, the time was longer both in synthesis of 5a or 6a.

3. Experimental section

3.1. Chemicals

Chemical reagents and solvents were purchased from the Merck and Aldrich Companies. MWCNTs (purity >95%) were prepared from Shenzhen Nanotech Port Co. Ltd. with diameters and lengths ranging between 40 and 60 nm and 5 and 15 μm, respectively. FTIR spectra were recorded using a Perkin-Elmer FTIR 550 Spectrometer. Melting points were determined in open capillaries using an Electro thermal DRX-400 spectrometer at 400 MHz. The elemental analyses were obtained from a Carlo ERBA Model EA 1108 analyzer carried out on Perkin-Elmer 240c analyzer.
Ultrasoundation was performed in a BANDELIN ultrasonic HD 3200 instrument with probe model US 70/T with diameter of 6 mm that was immersed directly into the reaction mixture. The operating frequency was 20 KHz and the output power was 60–75 W through manual adjustment. Raman spectroscopy was recorded using FRA/106/S and SEM images prepared using 360 Cambridge instrument.

### 3.2. Preparation of MWCNTs@meglumine

0.6 g of pristine MWCNTs was refluxed for 4 h in 200 mL of 3:2 mixture of concentrated sulfuric and nitric acid. Then, the reaction mixture was filtered through a 10-μm pore size polycarbonate filter paper. After that, the filtrate was washed with distilled water until no residual acid was presented. Finally, the oxidized CNTs were dried in 80°C for 10 h.

**Scheme 3.** The reaction mechanism for the preparation of 1,4-DHPs in the presence of MWCNTs@meglumine.

**Figure 8.** The reusability of catalyst.
| Entry | Catalyst                        | Time (min) | Yield (%) | Product Ref. |
|-------|--------------------------------|------------|-----------|--------------|
| 1     | Nickel nanoparticle            | 1.5        | 89        | 6a           |
| 2     | MgO Nanoparticles              | 200        | 73        | 5a           |
| 3     | Without catalyst               | 10         | 61        | 5b           |
| 4     | Melamine trisulfonic acid      | 210        | 94        | 5a           |
| 5     | SSA@IL                         | 15         | 90        | 5b           |
| 6     | Silica (NPs) supported Fe (III)| 20         | 94        | 65           |
| 7     | Nano ZnO                       | 60         | 78        | 5a           |
| 8     | Nano-γ-alumina                 | 45         | 70        | 5a           |
| 9     | Nano-ZMS-S²                   | 50         | 75        | 5a           |
| 10    | Nanocrystalline S²             | 45         | 80        | 5a           |
| 11    | V-TiO₂                         | 15         | 80        | 6a           |
| 12    | SBA-pr-SO₃H                   | 10         | 85        | 6a           |
| 13    | MWNTs@megulmine                | 15         | 95        | This work    |
| 14    | MWNTs@megulmine                | 18         | 92        | This work    |

*Reaction was performed under microwave irradiation;  
*Reaction was performed under visible light;  
Silica functionalized sulfonic acid coated with ionic liquid;  
Alumosilicic zealite belonging;  
Nano-crystalline sulfated zirconia;  
Mesoporous vanadium ion doped titania nanoparticles.

After the oxidation of MWCNTs, to make the MWCNTs-COOCl, 0.5 g of the oxidized MWNTs were stirred in 120 mL of thionyl chloride at 65°C for 24 h to convert the carboxylic acid groups into acyl chlorides. After the completion of reaction, the reaction mixture was filtered (through a 10-µm pore size polycarbonate filter paper), washed with distilled water, and finally dried in 90°C.

In the last step of preparation of supported catalyst, 0.45 g of acylated CNTs and 4 g of meglumine was stirred in 50 mL of DMF at 100°C for 12 h. In this reaction, the mixture was cooled to room temperature and 10 mL distilled water was added. After filtration, the resulting mixture was filtered and washed with distilled water for removing the untreated meglumine and finally dried at 90°C.

As shown in Scheme 2, the attachment of meglumine to surfaces of CNTs was performed through a nucleophilic substitution reaction. In fact, terminal hydroxyl group and N atom in the meglumine structure can be easily attacked by nucleophile to acyl groups on CNT surfaces.

### 2.3. General procedure for synthesis 1,4-DHPs

A mixture of 1 mmol aryl aldehyde, 1 mmol ammonium acetate, 2 mmol ethylacetoacetate (or 1 mmol ethylacetatoacetate and 1 mmol of dimedone) in 2 mL of ethanol was prepared and 0.02 g of MWCNTs@megulmine was added as catalyst. Reaction mixture was equipped with ultrasonic probe under the power of 70 W. The reaction progress was monitored by TLC. After the completion of reaction, the reaction mixture was cooled to room temperature, CH₂Cl₂ was added, and the heterogeneous catalyst was separated by simple filtration. The filtrate was concentrated to dryness, and the crude solid product was recrystallized from EtOH. All of 1,4-DHP products were identified by physical and spectroscopic data.

#### 3,5-diethoxy carbonyl-4-(4-nitro) phenyl-2,6-dimethyl-1,4-dihydropyridine (5a)

M.p.: 127–129°C; FTIR (KBr): ν = 3321 (N–H), 1700 (C=O), 1646 (C=C), 1486 (N–H), 1345 (C–H Bending CH₃), 1216 (C–O), 704 (C–H Bending aromatic cm⁻¹); ¹H NMR (CDCl₃, 400 MHz): δ = 1.21 (t, J = 7.2 Hz, 4H, 2CH₃), 3.15 (s, 3H, OCH₃), 4.07–4.09 (q, J = 4 Hz, 4H, 2CH₂), 5.08 (s, 1H, CH), 5.81 (s, 1H, NH), 7.43–8.08 (m, 4H, H-Aromatic) ppm; MS (m/z): 373.97 (M⁺).

#### 3,5-diethoxy carbonyl-4-(4-methoxy) phenyl-2,6-dimethyl-1,4-dihydropyridine (5b)

M.p.: 156–158°C; FTIR (KBr): ν = 3342 (N–H), 1690 (C=O), 1650 (C=C), 1490 (N–H), 1210 (C–O), 749 (C–H Bending aromatic cm⁻¹); ¹H NMR (CDCl₃, 400 MHz): δ = 1.22 (t, J = 7.2 Hz, 6H, 2CH₃), 2.32 (s, 6H, 2CH₃), 3.75 (s, 3H, OCH₃), 4.08 (m, 4H, 2CH₂), 4.92 (s, 1H, CH), 5.68 (s, 1H, NH), 6.74–7.27 (m, 4H, H-Aromatic) ppm; MS (m/z): 359.01 (M⁺).

#### 3,5-diethoxy carbonyl-4-(4-chloro) phenyl-2,6-dimethyl-1,4-dihydropyridine (5c)

M.p.: 144–146°C; FTIR (KBr): ν = 3356 (N–H), 1696 (C=O), 1651 (C=C), 1486 (N–H), 1375 (C–H Bending CH₃), 1213 (C–O), 829 (C–Cl), 744 (C–H Bending aromatic cm⁻¹); ¹H NMR (CDCl₃, 400 MHz): δ = 1.21 (t, J = 7.2 Hz, 4H, 2CH₂), 2.31 (s, 6H, 2CH₃), 4.08 (q, J = 5.2 Hz, 4H, 2CH₂), 4.95 (s, 1H, CH), 5.78 (s, 1H, NH), 7.20 (m, 4H, H-Aromatic) ppm; MS (m/z): 363.47 (M⁺).

#### 3,5-diethoxy carbonyl-4-(3-nitro) phenyl-2,6-dimethyl-1,4-dihydropyridine (5d)

M.p.: 163–165°C; FTIR (KBr): ν = 3344 (N–H), 1706 (C=O), 1646 (C=C), 1486 (N–H), 1345 (C–H Bending CH₃), 1212 (C–O), 703 (C–H Bending aromatic cm⁻¹); ¹H NMR (CDCl₃, 400 MHz): δ = 1.20 (t, J = 7.2 Hz, 6H, 2CH₃), 2.35 (s, 6H, 2CH₃), 4.11 (m, 4H, 2CH₂), 5.09 (s, 1H, CH), 5.95 (s, 1H, NH), 7.21–8.13 (m, 4H, H-Aromatic) ppm; MS (m/z): 342.00 (M⁺).

#### 3,5-diethoxy carbonyl-4-phenyl-2,6-dimethyl-1,4-dihydropyridine (5e)

M.p.: 156–158°C; FTIR (KBr): ν = 3341 (N–H), 1689 (C=O), 1650 (C=C), 1487 (N–H), 1375 (C–H Bending CH₃), 1247 (C–O), 737 (C–H Bending aromatic cm⁻¹); ¹H NMR (CDCl₃, 400 MHz): δ = 1.22 (t, J = 4 Hz, 6H, 2CH₃), 2.31 (s, 6H, 2CH₃), 4.05–4.11 (m, 4H, 2CH₂), 4.99 (s, 1H, CH), 5.79 (s, 1H, NH), 7.12–7.38 (m, 5H, H-Aromatic) ppm; MS (m/z): 329.00 (M⁺).

#### 3,5-diethoxy scarbonyl-4-(2-fluoro) phenyl-2,6-dimethyl-1,4-dihydropyridine (5f)

M.p.: 145–147°C; FTIR (KBr): ν = 3333 (N–H), 1649 (C=O), 1651 (C=C), 1489 (N–H), 1385 (C–H bending
3,5-diethoxy carbonyl-4-(4-methyl) phenyl- 2,6-dimethyl-1,4-dihydropyridine (5 g)

M.p.: 141–143°C; FTIR (KBr): νmax = 3339 (N=H), 1665 (C=O), 1483 (N–H), 1382 (C–H bending aliphatic), 1216 (C=O), 748 (C–H bending aromatic) cm⁻¹; ¹H NMR(CDCl₃, 400 MHz): δ = 1.12 (t, J = 6.8, 2 CH₃); 2.28 (s, 6H, 2CH₃); 4.12 (q, 4H, J = 2.4 Hz); 4.83 (s, 1H), 5.59 (s, 1H), 7.12–7.24 (m, 4H, Aromatic-H) ppm; MS (m/z): 407.91 (M⁺).

3,5-diethoxy carbonyl-4-(4-boromo) phenyl- 2,6-dimethyl-1,4-dihydropyridine (5 h)

M.p.: 146–148°C; FTIR (KBr): νmax = 3342 (N=H), 1680 (C=O), 1485 (N–H), 1386 (C–H bending aliphatic), 1216 (C=O), 652 (C=Br) cm⁻¹; ¹H NMR(CDCl₃, 400 MHz): δ = 1.21 (t, 6H, J = 14 Hz, 2CH₃); 2.28 (s, 6H, 2CH₃); 4.12 (q, 4H, J = 2.4 Hz); 4.83 (s, 1H), 5.59 (s, 1H), 7.12–7.24 (m, 4H, Aromatic-H) ppm; MS (m/z): 407.91 (M⁺).

3,5-diethoxy carbonyl-4-(3-Hydroxy) phenyl- 2,6-dimethyl-1,4-dihydropyridine (5i)

M.p.: 170–172°C; FTIR (KBr): νmax = 3346 (N=H), 1703 (C=O), 1606(C=C), 1491 (N–H), 1379 (C–H bending CH₃), 1216(C=O) cm⁻¹; ¹H NMR(CDCl₃, 400 MHz): δ = 0.86(s, 3H, CH₃), 1.12(s, 3H, CH₃), 1.24(t, J = 8.2 Hz, 2H, CH₂CH₃), 2.12–2.18(m, 4H, 2CH₂), 2.41(s, 3H, CH₃), 4.04(q, J = 7.2 Hz, 2H, CH₂CH₂), 5.15(s, 1H, CH), 6.02(s, 1H, N=H), 7.48(d, J = 8 Hz, 2H, H-Aromatic), 8.08(d, J = 7.6 Hz, 2H, H-Aromatic) ppm; MS (m/z): 383.97 (M⁺).

3,5-diethoxy carbonyl-4-(4-chloro)phenyl-2,7,7-trimethyl-5-oxo-1,4-dihydropyridine (6a)

M.p.: 238–240°C; FTIR (KBr): νmax = 3276(N=H), 1703 (C=O), 1606(C=C), 1491 (N–H), 1379 (C–H bending CH₃), 1216(C=O) cm⁻¹; ¹H NMR(CDCl₃, 400 MHz): δ = 0.86(s, 3H, CH₃), 1.12(s, 3H, CH₃), 1.24(t, J = 8.2 Hz, 2H, CH₂CH₃), 2.12–2.18(m, 4H, 2CH₂), 2.41(s, 3H, CH₃), 4.04(q, J = 7.2 Hz, 2H, CH₂CH₂), 5.15(s, 1H, CH), 6.02(s, 1H, N=H), 7.48(d, J = 8 Hz, 2H, H-Aromatic), 8.08(d, J = 7.6 Hz, 2H, H-Aromatic) ppm; MS (m/z): 383.97 (M⁺).

3,5-diethoxy carbonyl-4-(4-chloro)phenyl-2,7,7-trimethyl-5-oxo-1,4-dihydropyridine (6b)

M.p.: 231–233°C; FTIR (KBr): νmax = 3275(N=H), 1704 (C=O), 1605(C=C), 1490(N–H), 1380(C–H bending CH₃), 1216(C=O), 847(C–H bending aromatic), 640(C=C) cm⁻¹; ¹H NMR(CDCl₃,400 MHz): δ = 0.8 (s, 3H, CH₃), 0.95(s, 3H,CH₃), 1.1(t, J = 7 Hz, 3H, CH₃CH₂), 2.15–2.23(m, 4H, 2CH₂), 2.45(s, 3H, CH₃), 3.95(q, J = 6.8, 2H, CH₂CH₂), 4.8 (s, 1H, CH), 7.12(d, J = 8.4 Hz, 2H, H-Aromatic), 7.22(d, J = 8.4 Hz, 2H, H-Aromatic), 9.1(s, 1H, N–H) ppm; MS (m/z): 338.02 (M⁺).

3,5-diethoxy carbonyl-4-(3-nitro)phenyl-2,7,7-trimethyl-5-oxo-1,4-dihydropyridine (6c)

M.p.: 180–182°C; FTIR (KBr): νmax = 3283(N=H), 1703 (C=O), 1607(C=C), 1484(N–H), 1380(C–H bending CH₃), 1212(C=O), 721(C–H bending aromatic) cm⁻¹; ¹H NMR (CDCl₃,400 MHz): δ = 0.8 (s, 3H, CH₃), 0.99(s, 3H,CH₃), 1.1 (t, J = 7 Hz, 3H, CH₃CH₂), 1.95–2.3 (m, 4H, 2CH₂), 2.46(s, 3H, CH₃), 3.96(q, J = 2.4 Hz, 2H, CH₂CH₂), 4.94(s, 1H, CH), 7.5(t, J = 7.2 Hz, 1H, H-Aromatic), 7.59(d, J = 6.8 Hz, H-Aromatic), 7.95(t, J = 10.6 Hz, 2H, H-Aromatic), 9.25(s, 1H, N–H) ppm; MS (m/z): 383.95 (M⁺).
3-ethoxycarbonyl-4-(4-methyl)phenyl-2,7,7-trimethyl-5-oxo-1,4-dihydropyridine (6d)

M.p.: 254–256°C; FTIR (KBr): νmax = 3276(N–H), 1700 (C=O), 1605(C=C), 1491(N–H), 1380(C–H Bending CH3), 1216(C–O) cm⁻¹; 1H NMR(CDCl3, 400 MHz): δ = 0.92(s, 3H, CH3), 1.01(s, 3H, CH3), 1.24(t, J = 7 Hz, 3H, CH2CH3), 2.21–2.35(m, 4H, 2CH2), 2.38(s, 3H, CH3), 3.71 (s, 3H, CH3), 4.05(q, J = 6.8 Hz, 2H, CH2CH3), 5.1(s, 1H, CH), 6.01 (s, 1H, N–H), 6.75(d, J = 2.4 Hz, 1H, H-Aromatic), 7.25(d, J = 4 Hz, 1H, H-Aromatic), 7.15(d, J = 4.8 Hz, 2H, H-Aromatic) ppm; MS (m/z): 353.00 (M⁺). 

3-ethoxy carbonyl-4-(4-methoxy)phenyl-2,7,7-trimethyl-5-oxo-1,4-dihydropyridine (6e)

M.p.: 256–258°C; FTIR (KBr): νmax = 3277(N–H), 1700(C=O), 1605(C=C), 1495(N–H), 1380(C–H Bending CH3), 1217(C–O), 848(C–H Bending aromatic) cm⁻¹; 1H NMR(CDCl3, 400 MHz): δ = 0.91(s, 3H, CH3), 1.17(s, 3H, CH3), 1.2(t, J = 6.8 Hz, 3H, CH2CH3), 2.2–2.35(m, 4H, 2CH2), 2.39(s, 3H, CH3), 3.74(s, 3H, OCH3), 4.05(q, J = 7.2, 2H, CH2CH3), 5.0 (s, 1H, CH), 5.85(s, 1H, N–H), 6.73(d, J = 8.8 Hz, 2H, H-Aromatic), 7.2(d, J = 8.4 Hz, 2H, H-Aromatic) ppm; MS (m/z): 369.01 (M⁺). 

3-ethoxy carbonyl-4-phenyl-2,7,7-trimethyl-5-oxo-1,4-dihydropyridine (6f)

M.p.: 212–214°C; FTIR (KBr): νmax = 3289(N–H), 1698 (C=O), 1612(C=C), 1484(N–H), 1379(C–H Bending CH3), 1213(C–O), 697(C–H Bending aromatic) cm⁻¹; 1H NMR (CDCl3, 400 MHz): δ = 0.91(s, 3H, CH3), 1.32(s, 3H, CH3), 1.25(t, J = 7.2 Hz, 3H, CH2CH3), 2.15–2.32(m, 4H, 2CH2), 2.41(s, 3H, CH3), 4.03(q, J = 7.2 Hz, 2H, CH2CH3), 5.02(s, 1H, CH), 6.23(s, 1H, N–H), 7.04–7.31 (2H, H-Aromatic) ppm; MS (m/z): 339.00 (M⁺). 

4. Conclusion

1,4-DHPs derivatives were synthesized via Hantzsch condensation using MWCNTs@meglumine under ultrasonic irradiation at room temperature. Highly efficient and reusable catalyst, simplicity of experiment, short reaction times and the easy workup of products makes this method more attractive for the synthesis of 1,4-DHPs. Also, a new heterogeneous, highly efficient basic catalyst can be used in synthesis of other organic compounds.

Disclosure statement

No potential conflict of interest by the authors.

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References

[1] Bossert, F.; Meyer, H.W.; Wehinger, E. Angew. Chem. Int. Ed. 1981, 20, 762–769.
[2] Mannhold, R.; Jablonka, B.; Voigdt, W.; Schoenafinger, K.; Schravan, K. Eur. J. Med. Chem. 1992, 27, 299–235.
[3] Esfahani, M.N.; Moghadam, M.; Tangestaninejad, S.; Mirkhani, V.; Momeni, A.R. Angew. Chem. Int. Ed. 2006, 44, 720–7224.
[4] Loev, B.; Snader, K.M. J. Org. Chem. 1965, 30, 1914–1916.
[5] Tu, S.J.; Zhou, J.F.; Deng, X.; Cai, P.J.; Wang, H.; Feng, J.C. Chin. J. Org. Chem. 2001, 21, 313–316.
[6] Sabita, G.; Reddy, G.S.K.K.; Reddy, C.S.; Yadav, J.S. Tetrahedron Lett. 2003, 44, 4129–4131.
[7] Hilgeroth, A.; Lillie, H. Eur. J. Med. Chem. 2003, 38, 495–499.
[8] KLSA, V. Drugs Future. 1995, 20, 135–138.
[9] Dondoni, A.; Massi, A.; Minghini, E.; Bertolasi, V. Tetrahedron Lett. 2004, 60, 2311–2325.
[10] Hantzsch, A. Chem. Ber. 1881, 14, 1637–1638.
[11] Ugi, I. Pure Appl. Chem. 2001, 73, 187–191.
[12] Cariou, C.C.A.; Clarkson, G.J.; Shipman, M. J. Org. Chem. 2008, 73, 9762–9764.
[13] Domling, A.; Wang, W.; Wang, K. Chem. Rev. 2012, 112, 3083–3135.
