Scientific paper

Efficient One-Pot Synthesis of 1,4-Dihydropyridines Catalyzed by Magnetic $MnFe_2O_4$ Nanoparticles

Somayeh Moradi, Mohsen Moradian and Hossein Naeimi*

Department of Organic Chemistry, Faculty of Chemistry, University of Kashan, Kashan, Iran

** Corresponding author: E-mail: naeimi@kashanu.ac.ir*

Received: 10-27-2021

Abstract

The efficient one-pot synthesis of some 1,4-dihydropyridines is described by a condensation reaction of some aldehyde derivatives, ethyl acetoacetate and ammonium acetate in the presence of superparamagnetic manganese ferrite nanoparticles at 80 °C. The advantages of this protocol include selectivity, high purity of the products, excellent yields, short reaction times, ease of processing, and environmentally friendly conditions for the synthesis of 1,4-dihydropyridines. In addition, the catalyst can be recovered and reused in multiple runs without significantly reducing the product yield.

Keywords: 1,4-Dihydropyridine; $MnFe_2O_4$; Nanoparticles; Catalyst; Superparamagnetism

1. Introduction

Multicomponent reactions (MCRs) are a very attractive approach as well as an efficient and powerful tool for the synthesis of novel compounds and the discovery of new drugs.[1–6] In MCRs, three or more flexible and simple compounds are reacted to synthesize complex organic molecules from commercially available starting materials. The Hantzsch reaction is one of the most popular MCRs and generates 1,4-dihydropyridine (1,4-DHP) derivatives. This reaction, which has received considerable attention in modern synthetic organic chemistry, was first described by A. Hantzsch in 1882.[7] The Hantzsch reaction is a practical and useful synthetic tool for the preparation of 1,4-dihydropyridines by condensation of ethyl acetoacetate, an aldehyde, and a source of ammonia in the presence of an

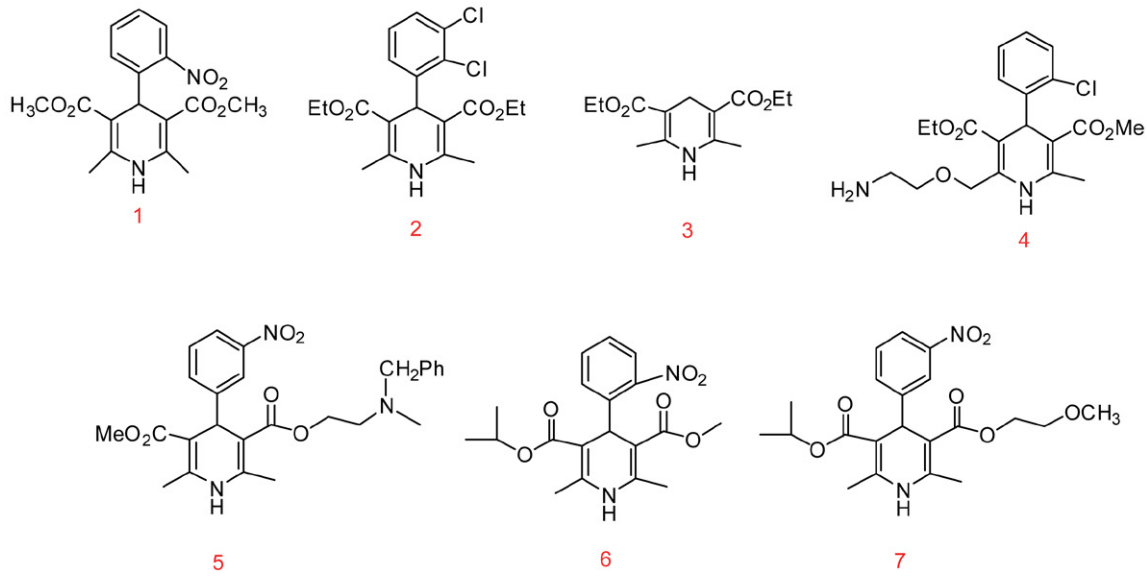


Figure 1. Some biologically active 1,4-dihydropyridines.

alcoholic solvent.[8] In modern synthetic organic chemistry, 1,4-dihydropyridines are an important group of drugs[9–11] and calcium channel modulators for the treatment of hypertension,[12] tumors,[13,14] HIV,[15] cancer,[16] diabetes,[17] apoptosis, and[18] seizures.[19] For example, nifedipine (1), felodipine (2), diludin (3), amlodipine (4), nicardipine (5), nisodipine (6), and nimodipine (7) are synthesized and used worldwide (Figure 1).

Recently, methods have been described using different types of catalysts such as $CeCl_3{\cdot}7H_2O$,[20] ionic liquids,[21,22] TBAB,[23] visible light,[24,25] chitosan silica sulfate,[26] molybdic acid-functionalized nano-Fe_3O_4@TiO_2,[27] $HClO_4$-SiO_2,[28] microwave-assisted,[29] PW/SiO_2,[30] solar thermal,[31] I2,[32] sulfonic acid,[33] Fe_3O_4@SiO_2@OSO_3H,[34] heteropolyacids,[35] silica gel/$NaHSO_4$,[36] organocatalysis,[37] $AlCl_3{\cdot}6H_2O$,[38] and metal triflates.[39] Although many of these methods are effective, the search for a more satisfactory catalyst is essential for the preparation of 1,4-DHP. Metal oxide nanocrystals, especially superparamagnetic ones, have recently been used as effective catalysts because of their easy availability and environmentally friendly properties.[40] Because of the advantages of magnetic nanoparticles, such as low-cost large-scale synthesis, easy separation and reuse using an external magnet, and applicability in industrial processes, their use as catalysts in various organic reactions has been developed.[41–47] In this research, we describe a useful and simple method for the preparation of 1,4-dihydropyridines from the condensation of ethyl acetoacetate, various aldehydes, and ammonium acetate as a source of ammonia using magnetic $MnFe_2O_4$ nanoparticles as a catalyst and ethanol as a solvent.

2. Experimental Section

2. 1. Apparatus

Chemical reagents and solvents were purchased commercially from Aldrich and Fluka Chemical Companies and used without further purification. A Bruker DRX-400 spectrometer was used to record ^1H NMR and ^{13}C NMR spectra in deuterated chloroform solvent. Infrared spectra (IR) were recorded as KBr pellets using a Nicolet Impact 400 FT-IR spectrophotometer. Elemental analyzes (C, H, and N) were performed using a Perkin Elmer 2400- CHN elemental analyzer. XRD patterns of samples with an X-ray wavelength of 1.54 °A and Cu anode material were recorded using a Philips X'PertPro X-ray diffractometer at a scanning speed of 2°/min over a range of 10° to 80° (2θ). The powder morphology of the catalyst was determined using a Hitachi S4160 as a field emission scanning electron microscope (FE-SEM). The magnetic properties of the nanoparticles were determined by vibrational magnetometric measurements (VSM, PPMS-9T) at 300 K in Iran (College of Kashan, Iran). The melting points were determined using a Yanagimoto micro-melting point apparatus. The course of the reaction was checked by thin layer chromatography (TLC) on silica gel polygram SILG/UV 254 plates.

2. 2. General Procedure for the Synthesis of $MnFe_2O_4$ NPs

$MnFe_2O_4$ nanoparticles were synthesized by simple coprecipitation of $FeCl_3/MnCl_2$ in alkaline NaOH medium. First, 100 ml solution of the two salts $FeCl_3{\cdot}6H_2O$ and $MnCl_2{\cdot}4H_2O$ were prepared such that the molar ratio of Mn^{2+}: Fe^{3+} molar ratio was 2:1. For this purpose, 0.02 mol of Fe(III) salt and 0.01 mol of Mn(II) salt were dissolved in distilled water and the volume of the solution was made up to 100 mL. Then, the desired solution was added dropwise into a solution of NaOH (100 mL, 3 mol L^{-1}) at 95 °C with constant stirring for 2 h. The solution was then added to the solution of NaOH (100 mL, 3 mol L^{-1}). At the end of the desired time, the solid was collected with an external magnetic field, washed with ethanol (3 × 20 mL) and deionized water (5 × 30 mL), and then dried at 60 °C for 12 h. The solid was then removed from the solution. The $MnFe_2O_4$ nanoparticles were characterized by physical and spectroscopic data.

2. 3. A General Method for the Synthesis of 1,4-dihydropyridines

A mixture of ethyl acetoacetate (2.4 mmol), selected aldehyde (1 mmol), NH_4OAc (1.2 mmol), and $MnFe_2O_4$ (5 mol%) in ethanol (5 mL) as solvent was stirred at 80 °C for an appropriate time. The progress of the reaction was followed by thin layer chromatography (TLC). After completion of the reaction, the mixture was diluted with ethyl acetate and the solid catalyst was separated and collected using a magnetic field. The desired product was extracted with ethyl acetate and water and purified by recrystallization from ethanol/water (5:1) to afford pure 1,4-dihydropyridines. The solid magnetic $MnFe_2O_4$ catalyst was carefully washed with acetone (3 × 10 ml) and distilled water (3 × 10 ml), and dried at room temperature in a desiccator. The structure of the new compounds was identified from the physical and spectroscopic data.

2. 4. Spectral Data for 1,4-dihydropyridine Derivatives

Diethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4a); Yellow solid; m.p. = 162–167 °C; IR (KBr, cm^{-1}) ν: 3344 (NH), 3093 (=CH_2), 2987 (-CH, sp^3), 1706 (C=O), 1645 (C=C), 1213 (C-O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ: 1.23 (t, *J*=7.2 Hz, 6H, $2CH_3$), 2.36 (s, 6H, $2CH_3$), 4.08 (q, 4H, $2CH_2$), 5.08 (s, 1H), 5.86 (s, 1H, NH), 7.37 (t, *J*=8 Hz, 1H, ArH), 7.64 (d, *J*=7.6 Hz, 1H, ArH), 7.99 (d, *J*=7.2 Hz, 1H, ArH), 8.12 (s, 1H, ArH).

Diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (4b); Yellow solid; m.p. = 150–155 °C; IR

(KBr, cm^{-1}) ν: 3342 (NH), 3061 (=CH_2), 2980 (-CH, sp^3), 1690 (C=O), 1651 (C=C), 1211 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 1.22 (t, *J*=7.2 Hz, 6H, $2CH_3$), 2.33 (s, 6H, $2CH_3$), 4.10 (q, 4H, $2CH_2$), 4.98 (s, 1H), 5.66 (s, 1H, NH), 7.10–7.27 (m, 5H, ArH).

Diethyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4c); Light yellow solid; m.p. = 125–128 °C; IR (KBr, cm^{-1}) ν: 3320 (NH), 3101 (=CH_2), 2980 (-CH, sp^3), 1701 (C=O), 1646 (C=C), 1214 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 1.21 (t, *J*=7.2 Hz, 6H, $2CH_3$), 2.36 (s, 6H, $2CH_3$), 4.06 (q, 4H, $2CH_2$), 5.09 (s, 1H), 5.74 (s, 1H, NH), 7.44 (d, *J*=8.8 Hz, 2H, ArH), 8.07 (d, *J*=8.8 Hz, 2H, ArH).

Diethyl 4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4d); Yellow solid; m.p. = 140–145 °C; IR (KBr, cm^{-1}) ν: 3356 (NH), 3091 (=CH_2), 2988 (-CH, sp^3), 1696 (C=O), 1651 (C=C alkene), 1213 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 1.22 (t, *J*=6.8 Hz, 6H, $2CH_3$), 2.32 (s, 6H, $2CH_3$), 4.08 (q, 4H, $2CH_2$), 4.95 (s, 1H), 5.70 (s, 1H, NH), 7.16 (d, *J*=8.8 Hz, 2H, ArH), 7.21 (d, *J*=8.4 Hz, 2H, ArH).

Diethyl 4-(2-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4e); White solid. m.p. = 118–120 °C; IR (KBr, cm^{-1}(ν: 3325 (NH), 3060 (=CH_2), 2978 (-CH, sp^3), 1699 (C=O), 1671 (C=C), 1613, 1491 (C=C, Ar), 1206 (C-O); ^{1}H NMR ($CDCl_3$, 400 MHz, δ / ppm): 1.20 (t, *J*=7.2 Hz,6H, $2CH_3$), 2.31 (s, 6H, $2CH_3$), 4.07 (q, 4H, $2CH_2$), 5.39 (s, 1H), 5.65 (s, 1H, NH), 7.04 (t, *J*=7.6 Hz,1H, ArH), 7.12 (t, J=7.6 Hz,1H, ArH), 7.22 (d, *J*=8 Hz, 1H, ArH), 7.37 (d, *J*=1.6 Hz, 1H, ArH).

Diethyl 4-(2,4-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4h); Yellow solid; m.p = 140–142 °C; IR (KBr, cm^{-1}(ν: 3378 (NH), 3087 (=CH_2), 2980 (-CH, sp^3), 1699 (C=O), 1679 (C=C), 1617, 1494 (C=C, Ar), 1201 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 1.20 (t, *J*=7.2 Hz, 6H, $2CH_3$), 2.31 (s, 6H, $2CH_3$), 4.07 (q, 4H, $2CH_2$), 5.35 (s, 1H), 5.61 (s, 1H, NH), 7.10 (d, *J*=7.6 Hz, 1H, ArH), 7.25 (s, 1H, ArH), 7.31 (d, *J*=8.0 Hz, 1H, ArH).

Diethyl 4-(3-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4l); Yellow solid; m.p. = 119–123 °C; IR (KBr, cm^{-1}) ν: 3342 (NH), 3095 (=CH_2), 2983 (-CH, sp^3), 1699 (C=O), 1649 (C=C), 1605, 1487 (C=C, Ar), 1215 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 1.23 (t, *J*=7.2 Hz, 6H, $2CH_3$), 2.32 (s, 6H, $2CH_3$), 3.76 (s, 3H, CH_3), 4.11 (q, 4H, $2CH_2$), 4.98 (s, 1H), 5.72 (s, 1H, NH), 6.67 (d, *J*=8.8 Hz, 1H, ArH), 6.84 (s, 1H, ArH), 6.89 (d, *J*=6.8 Hz, 1H, ArH), 7.13 (t, *J*=8.0 Hz, 1H, ArH).

Diethyl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4j); White solid; m.p. = 150–155 °C; IR (KBr, cm^{-1}) ν: 3343 (NH), 2983 (-CH, sp^3), 1689 (C=O), 1650 (C=C), 1210 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 1.23 (t, *J*=7.2 Hz, 6H, $2CH_3$), 2.32 (s, 6H, $2CH_3$), 3.75 (s, 3H, CH_3), 4.09 (q, 4H, $2CH_2$), 4.93 (s, 1H), 5.60 (s, 1H, NH), 6.75 (d, *J*=8.8 Hz, 2H, ArH), 7.20 (d, *J*=8.4 Hz, 2H, ArH).

Diethyl 4-(4-fluorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4i); Yellow solid; m.p. = 145–147 °C; IR (KBr, cm^{-1}) ν: 3343 (NH), 3068 (=CH_2), 2983(-CH, sp^3), 1688 (C=O), 1652 (C=C), 1210 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 1.21 (t, *J*=7.2 Hz, 6H, $2CH_3$), 2.33 (s, 6H, $2CH_3$), 4.04 (q, 4H, $2CH_2$), 4.95 (s, 1H), 5.67 (s, 1H, NH), 6.88 (t, *J*=8.4 Hz, 2H, ArH), 7.23 (t, *J*=5.6 Hz, 2H, ArH).

Diethyl 4-(2-bromophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4f); Yellow solid; m.p. = 128–131 °C; IR (KBr, cm^{-1}) ν: 3325 (NH), 3058 (=CH_2), 2978 (-CH, sp^3), 1698 (C=O), 1673 (C=C), 1613 , 1490 (C=C, Ar),1208 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 1.20 (t, *J*=7.2 Hz, 6H, $2CH_3$), 2.30 (s, 6H, $2CH_3$), 4.08 (q, 4H, $2CH_2$), 5.36 (s, 1H), 5.62 (s, 1H, NH), 6.96 (t, *J*=8.8 Hz,1H, ArH), 7.17 (t, *J*=7.2 Hz, 1H, ArH), 7.38 (d, *J*=1.6 Hz, 1H, ArH), 7.42 (d, *J*=8.0 Hz,1H, ArH).

Diethyl 4-(4-(dimethylamino) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3k); Yellow solid; m.p. = 195–200 °C; IR (KBr, cm^{-1}) ν: 3321 (NH), 3094(=CH_2), 2978 (-CH, sp^3), 1695 (C=O), 1674 (C=C), 1492, 1613 (C=C, Ar), 1203 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 1.24 (t, *J*=7.2 Hz, 6H, $2CH_3$), 2.32 (s, 6H, $2CH_3$), 2.89 (s, 6H, CH_3), 4.08 (q, 4H, $2CH_2$), 4.88 (s, 1H), 5.65 (s, 1H, NH), 6.61 (d, *J*=8.4 Hz, 2H, ArH), 7.17 (d, *J*=7.2 Hz, 2H, ArH).

Diethyl 2,6-dimethyl-4-(p-tolyl)-1,4-dihydropyridine-3,5-dicarboxylate (4o); White solid; m.p. = 139–140 °C; IR (KBr, cm^{-1}) ν: 3358 (NH), 2986 (-CH, sp^3), 1695 (C=O), 1652 (C=C), 1203 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 1.23 (t, *J*=7.2 Hz, 6H, $2CH_3$), 2.27 (s, 3H, CH_3), 2.32 (s, 6H, $2CH_3$), 4.08 (q, 4H, $2CH_2$), 4.95 (s, 1H), 5.62 (s, 1H, NH), 7.01 (d, *J*=7.6 Hz, 2H, ArH), 7.17 (d, *J*=8.0 Hz, 2H, ArH).

Diethyl 4-(2-fluorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4g); Yellow solid; m.p. = 155–157 °C; IR (KBr, cm^{-1}) ν: 3332 (NH), 3104 (=CH_2), 2982 (-CH, sp^3), 1694 (C=O), 1651 (C=C), 1215 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 1.19 (t, *J*=7.2 Hz, 6H, $2CH_3$), 2.31 (s, 6H, $2CH_3$), 4.03 (q, 4H, $2CH_2$), 5.24 (s, 1H), 5.70 (s, 1H, NH), 6.92(t, *J*=9.6 Hz, 1H, ArH), 6.99 (t, *J*=7.6 Hz, 1H, ArH), 7.08 (t, *J*=7.2 Hz, 1H, ArH), 7.30 (t, *J*=7.2 Hz, 1H, ArH).

Diethyl 2',6'-dimethyl-1',4'-dihydro-[2,4'-bipyridine]-3',5'-dicarboxylate (4n); Brown solid; m.p. = 188–191 °C; IR (KBr, cm^{-1}) ν: 3172 (NH), 2982 (-CH, sp^3), 1695 (C=O), 1670 (C=C), 1478, 1639 (C=C, Ar), 1212 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 1.20 (t, *J*=7.2 Hz, 6H, $2CH_3$), 2.26 (s, 6H, $2CH_3$), 4.05 (q, 4H, $2CH_2$), 5.20 (s, 1H), 7.17 (d, *J*=5.2 Hz, 1H, ArH), 7.43(d, *J*=6.8 Hz, 1H, ArH), 7.62(t, *J*=7.2 Hz, 1H, ArH), 8.51 (d, *J*=4.4 Hz, 1H, ArH), 8.71(s, 1H, NH).

Diethyl 4-(3-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4m); White solid; m.p. = 168–170 °C; IR (KBr, cm^{-1}) ν: 3351 (NH), 2978 (-CH, sp^3), 1651 (C=O), 1593 (C=C), 1217 (C-O); ^{1}H NMR (400

MHz, $CDCl_3$, ppm) δ: 1.23 (t, *J*=7.2 Hz, 6H, $2CH_3$), 2.32 (s, 6H, $2CH_3$), 4.10 (q, 4H, $2CH_2$), 4.97 (s, 1H), 5.71 (s, 1H, NH), 6.62(d, *J*=7.2 Hz, 1H, ArH), 6.78(s, 1H, ArH), 6.87 (d, *J*=7.2 Hz, 1H, ArH), 7.07(t, *J*=7.6 Hz, 1H, ArH).

Diethyl 4-(9,10-dioxo-9,10-dihydroanthracen-2-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3p); Brown solid; m.p. = 195–200 °C; IR (KBr, cm^{-1}) ν: 3293 (NH), 2983 (-CH, sp^3), 1670 (C=O), 1637 (C=C), 1214 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 1.20 (t, *J*=7.2 Hz, 6H, $2CH_3$), 2.32 (s, 6H, $2CH_3$), 4.05 (q, 4H, $2CH_2$), 5.33 (s, 1H), 6.17 (s, 1H, NH), 7.74(m, 4H, ArH), 8.01(d, *J*=8.0 Hz, 1H, ArH), 8.21 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 15.23, 20.18, 41.58, 62.81, 102.05, 126.94, 130.68, 131.36, 132.62, 133.87, 134.18, 134.94, 135.25, 144.76, 152.63, 167.54, 181.94. Anal. Calcd. for $C_{27}H_{25}NO_6$: C, 70.58; H, 5.48; N, 3.05. Found: C, 70.91; H, 5.51; N, 3.07.

3. Results and Discussion

3. 1. Characterization of $MnFe_2O4$ Nanocrystals.

Exploring new efficient strategies for the synthesis of organic compounds is a crucial approach for the expansion of science and technology. In this research, a magnetic nanoparticle catalyst was used in the Hantzsch reaction to prepare 1,4-dihydropyridine derivatives (DHP) in high yield. Superparamagnetic $MnFe_2O_4$ nanocrystals prepared from $MnCl_2$ and $FeCl_3$ via a co-precipitation routine were confirmed and characterized by a vibrating magnetometer (VSM), a scanning electron microscope (SEM), Fourier transform infrared spectroscopy (FT-IR), and X-ray diffraction (XRD). Figure 2 shows the FT-IR spectra of magnetic $MnFe_2O_4$ nanoparticles. The FT-IR spectrum shows an absorption band at about 550 cm^{-1} related to the Fe-O stretching vibration. It also shows a band at 1621 cm^{-1}, which is due to the O-H deformation vibration, and a band at 3403 cm^{-1}, which is from the O-H stretching vibration and is related to the surface hydroxyl groups and physisorbed water.

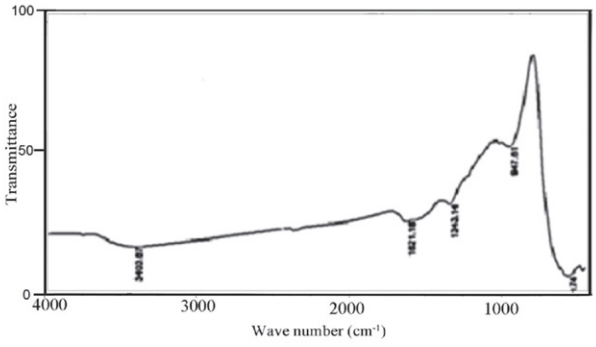


Figure 2. FT-IR spectra of $MnFe_2O_4$ nanoparticles.

Intensity and position of all peaks agreed well with the standard $MnFe_2O_4$ X-ray diffraction pattern (JCPDS chart No. 73-1964), and the particle size of about 33 nm was estimated from the line broadening at half maximum intensity (FWHM) at 2θ = 35.31 using Debye–Scherrer equation; D = 0.9λ/β Cosθ (Figure 3).

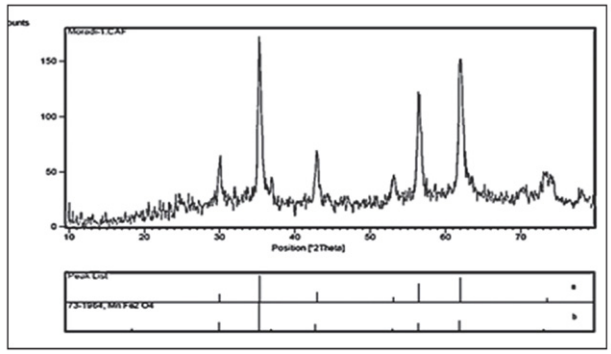


Figure 3. The X-ray diffraction patterns of the prepared $MnFe_2O_4$ NPs.

The micro- and nanoscale size and morphology of $MnFe_2O_4$ were studied by scanning electron microscopy (SEM). As Figure 4 shows, $MnFe_2O_4$-NP were spherical particles with an average size in the range of 33–35 nm.

VSM measures the magnetic properties of $MnFe_2O_4$ nanoclusters; hysteresis loops of $MnFe_2O_4$ nanoparticles were checked using a vibrating sample magnetometer (VSM). Figure 5 shows that the magnetization loop of MNPs exhibits superparamagnetic property with magnetization saturation of 57 emu g^{-1}. The superparamagnetism of MNPs is very advantageous because the particles are magnetized in an existing external magnetic field but show no magnetization in the absence of a magnet. Therefore, they are highly dispersed in the reaction medium and allow rapid penetration of reactants to the surface of the nanoparticles as an efficient catalyst.

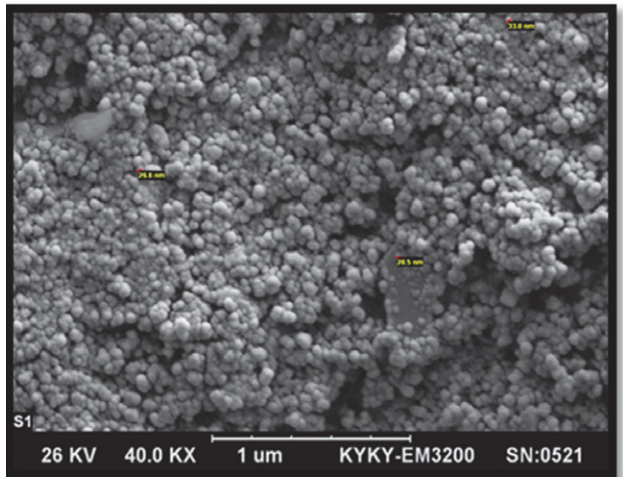


Figure 4. SEM image of $MnFe_2O_4$ nanoparticles.

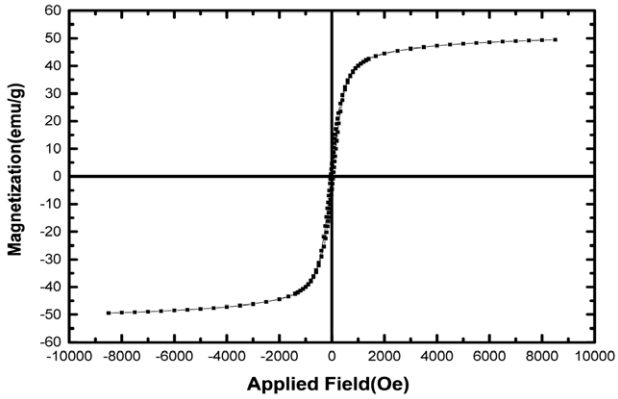


Figure 5. Magnetization curves of the prepared $MnFe_2O_4$ nanoparticles.

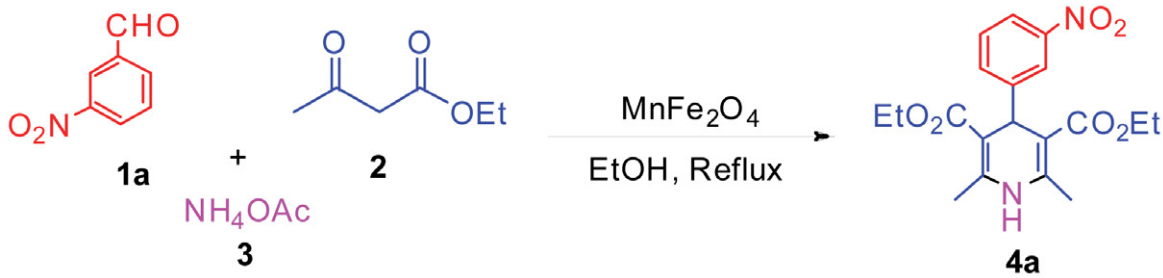
Table 1. Optimization of the reaction conditions. [a]

Entry	Catalyst (mol %)	Solvent	T (°C)	Time (min)	Yield (%)[b]
1	2	EtOH	78	120	75
2	4	EtOH	78	80	85
3	5	EtOH	78	45	95
4	8	EtOH	78	45	95
5	5	H_2O	80	45	80
6	5	THF	60	130	55
7	5	CH_3CN	80	150	45
8	5	EtOH	60	80	80
9	5	EtOH	70	60	85
10	5	EtOH	78	45	95
11	5	EtOH	90	50	95

[a] Reaction conditions: aldehyde (1 mmol), ethyl acetoacetate (2.4 mmol), ammonium acetate (1.2 mmol). [b] Isolated yields.

3. 2. Optimization and Generalization of Reaction Conditions

To investigate the catalytic activity of $MnFe_2O_4$ MNP catalysts, their catalytic performance in the reaction of ethyl acetoacetate (**1**), 3-nitrobenzaldehyde (**2**), and ammonium acetate (**3**) was studied (see Scheme 1).



Scheme 1. Model reaction for the synthesis of diethyl-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate.

To optimize the reaction, the influence of different polar solvents tested for the preparation of 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine-3,5-dicarboxylate was first investigated. Among the solvents used, such as acetonitrile (CH_3CN), ethanol, THF, and H_2O, EtOH is the most suitable for this reaction according to the data in Table 1, entries 5–7, because it is polar and protic (Table 1, entry 3)

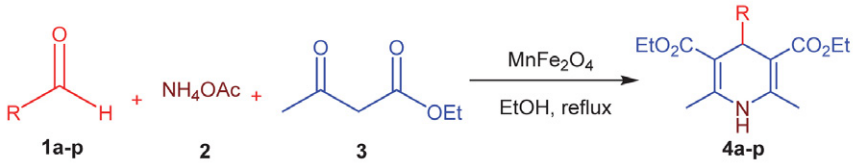
Different amounts of catalyst (2, 4, 5, and 8 mol%) were used to optimize the amount of catalyst. It was found that 5 mol% catalyst loading gave the highest yield in the shortest possible time (Table 1, entry 3). Therefore, the optimum catalyst loading was set at 5 mol% $MnFe_2O_4$ NPs.

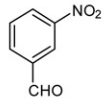
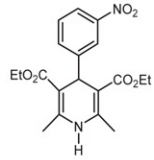
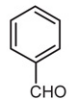
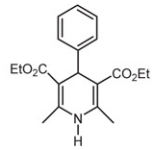
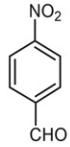
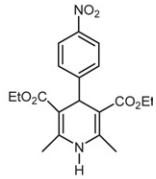
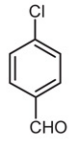
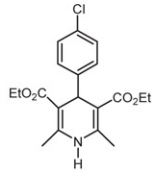
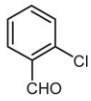
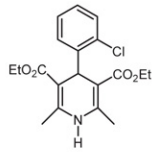
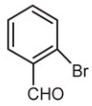
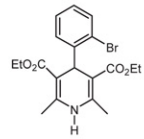
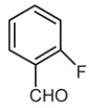
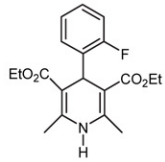
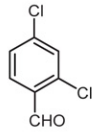
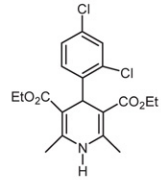
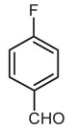
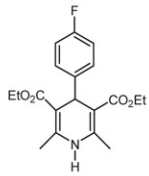
To determine the optimum reaction temperature, the sample reaction was carried out at 60 to 90 °C (Table 1, entries 8–11). From the results, it was concluded that the highest yield in the shortest possible time for the synthesis of the product was obtained at a reflux temperature of 78 °C (Table 1, entry 10).

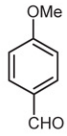
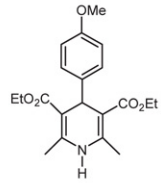
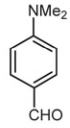
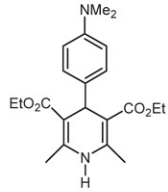
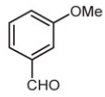
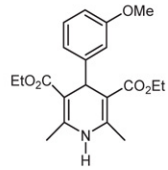
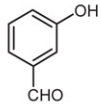
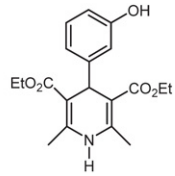
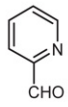
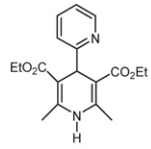
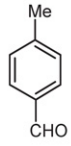
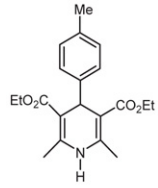
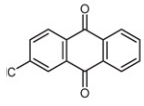
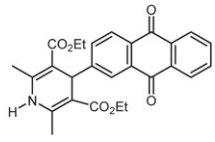
In this study, the reaction for the synthesis of various 1,4-dihydropyridines using $MnFe_2O_4$ nanoparticles as a heterogeneous catalyst was carried out to develop the scope and generality of this method considering the optimal reaction conditions. In this step, some aromatic functionalized derivatives of aldehydes with both electron donating and electron withdrawing properties were used for the reaction. The corresponding results are summarized in Table 2. It is noteworthy that the benzaldehyde derivatives with electron-withdrawing functional groups, such as 3-nitrobenzaldehyde and 4-chlorobenzaldehyde, etc., gave excellent yields of the corresponding products (Table 2, entries 1, 3–9), compared with an electron-donating group, which has a lower yield in the reaction (Table 2, entries 10–13).

The structure of $MnFe_2O_4$ is a mixed spinel that has a close packing of face-centered cubic lattices. The octahedral (Oh) and tetrahedral (Td) sites are occupied by Mn^{2+} and Fe^{3+} cations. The Oh sites are occupied by $Mn_x^{2+}Fe_{2-x}^{3+}$, and the metal ions are coordinated with six oxygen atoms, and the Td sites are occupied by $Mn_{1-x}^{2+}Fe_x^{3+}(0 < x < 1)$, and the metal ions are coordinated with four oxygen atoms. Since the Td sites have low

Table 2. Synthesis of different 1,4-dihydropyridines from several aldehydes.



Entry	Aldehyde	Product		Time (min)	Yield (%)[b]	Ref.
1			**4a**	45	95	[50]
2			**4b**	40	90	[51]
3			**4c**	45	95	[51]
4			**4d**	40	92	[50]
5			**4e**	50	89	[50]
6			**4f**	40	91	[52]
7			**4g**	40	90	[52]
8			**4h**	45	92	[53]
9			**4i**	40	91	[52]

Entry	Aldehyde	Product		Time (min)	Yield (%)[b]	Ref.
10			**4j**	70	88	[51]
11			**4k**	60	85	[50]
12			**4l**	70	87	[35]
13			**4m**	50	90	[50]
14			**4n**	45	90	[54]
15			**4o**	80	82	[54]
16			**4p**	50	82	–

– [a] Reaction conditions: aldehyde (1 mmol), ethyl acetoacetate (2.4 mmol), ammonium acetate (1.2 mmol), and $MnFe_2O_4$ (5 mol%) in ethanol (5 ml) as solvent at 78 °C. [b] Isolated yield.

steric hindrance compared to the Oh sites, the Mn atoms can act as more effective Lewis acid sites. The interaction between the Mn atoms of the nanocatalyst and the active sites of the substrate is more favorable.[48,49]

In agreement with the reaction mechanism proposed by some research groups,[55–57] the role of the nanocatalyst can be explained as follows. The activation of the electrophilic components of the carbonyl groups of aldehyde and acetoacetate adducts by Lewis acid moieties on the magnetic nanoparticles could be the driving force of the reaction. The first step involves the condensation of benzaldehyde and the enol form of ethyl acetoacetate to form the Knoevenagel adduct. At the same time, another intermediate is formed by the reaction of ammonia from ammonium acetate with the second equivalent of ethyl acetoacetate. Subsequently, the two intermediates formed in the above steps are reacted with each other, and the subsequent cyclocondensation and dehydration give the 1,4-dihydropyridine as the target product.

To emphasize the value of this study, the results obtained were compared with recently published work in Table 3. For this comparison, reaction conditions, reaction time and yield were considered in the synthesis of product **4b**. It is worth noting that the efficiency of $MnFe_2O_4$ NPs

as catalyst in this method is higher and easier to handle than some of the reported methods (Table 3, entry 11 versus entries 1–10).

Table 3. Comparison of the synthesis of 1,4-DHP (**4b**) using $MnFe_2O_4$ NPs with methods described in the literature.

Entry	Catalyst (amount)	Reaction conditions	Time (min)	Yield (%)	Ref.
1	$CeCl_3{\cdot}7H_2O$ (10 mol %)	H_3CCN, r.t.,	180	80	[20]
2	$[HMIM]BF_4$ (Excess)	90 °C	10	95	[21]
3	$[(CH_2)_4SO_3HMIM][HSO_4]$ (25 mol %)	C_2H_5OH, reflux	67	90	[22]
4	$MgBr_2$ (10 mol %)	solvent-free, 100 °C	45	82	[23]
5	$HClO_4$–SiO_2 (50 mg)	solvent-free, 80 °C	25	90	[28]
6	I_2 (30 mol %)	C_2H_5OH, r.t.,	150	93	[32]
7	SiO_2–SO_3H (0.2 g)	*n*-Hexane, 60 °C	330	90	[33]
8	$H_{14}[NaP_5W_{30}O_{110}]$ (0.01 g)	water, reflux	480	76	[35]
9	$NaHSO_4$–SiO_2 (5 mol %)	H_3CCN, r.t.,	360	85	[36]
10	$AlCl_3{\cdot}6H_2O$ (10 mol %)	solvent-free, 60 °C	60	80	[38]
11	$MnFe_2O_4$ NPs (5 mol %)	C_2H_5OH, 78 °C	45	95	This work

The reusability of the magnetic $MnFe_2O_4$ nanocatalyst, as shown in Figure 6, was investigated using the desired reaction under optimized conditions. The catalyst was isolated by an external magnet after each reaction and then carefully washed 3–4 times with ethanol and acetone. The catalyst was dried at a temperature of 60 °C and used five times without significant loss of catalytic activity. The weight percentage recovery of the catalyst after the reaction shows a negligible weight loss of about 0.3% and > 99.7% of the catalyst was recovered.

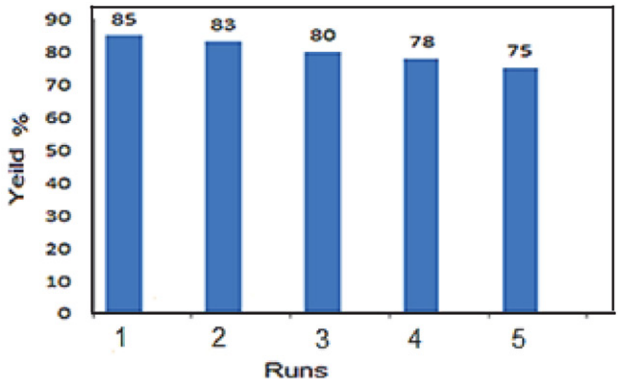


Figure 6. Reusability of the $MnFe_2O_4$ nanoparticles as catalyst.

4. Conclusion

In this protocol, we synthesized superparamagnetic $MnFe_2O_4$ nanoparticles and used them as an efficient catalyst in the synthesis of 1,4-dihydropyridines by one-pot condensation of aldehydes, ethyl acetoacetate, and ammonium acetate. The advantages of this method include high purity, good yield, simple work-up procedures, mild reaction conditions, short reaction times, magnetic separation of the catalyst with a permanent magnet, and reusability of the catalyst five times without significant deterioration of its activity.

Acknowledgments

We thank the Research Council of the University of Kashan for supporting this work through grant No. 159148/71.

Declarations: Funding: This research was funded by University of Kashan by grant No. 159148/71.

Conflict of interest: The authors declare that they have no conflict of interest.

5. References

1. H. Christopher, G. Vijay. *Curr. Med. Chem.* **2003** *10*, 51–80. **DOI:**10.2174/0929867033368600
2. M. C. Bagley, M. C. Lubinu. in *Top. Heterocycl. Chem.* (eds Erik Van der Eycken, C. Oliver Kappe), Springer Berlin Heidelberg, 2006, pp. 31–58.
3. H. Naeimi, S. Mohammadi. *J. Heterocycl. Chem.* **2020** *57*, 50–59. **DOI:**10.1002/jhet.3742
4. Z. Ghanbari, H. Naeimi. *J. Heterocycl. Chem.* **2021**, *58*, 1058–1069. **DOI:**10.1002/jhet.4236
5. M. Moradian, M. Nazarabi. *Acta Chim. Slov.* **2021**, *68*, 594–604. **DOI:**10.17344/acsi.2020.6412
6. H. Naeimi, A. Raeisi, M. Moradian. *Arab. J. Chem.* **2017**, *10*, S2723–S2728. **DOI:**10.1016/j.arabjc.2013.10.017
7. A. Hantzsch. *Justus Liebigs Ann. Chem.* **1882**, *215*, 1–82. **DOI:**10.1002/jlac.18822150102
8. J.-J. Xia, G.-W. Wang. *Synthesis* **2005**, 2379–2383. **DOI:**10.1055/s-2005-870022
9. V. K. Sharma, S. K. Singh. *RSC Adv.* **2017**, *7*, 2682–2732. **DOI:**10.1039/C6RA24823C
10. M. Ziaie, K. Akbaridilmaghani, A. Tukmechi. *Acta Chim. Slov.* **2017**, *64*, 895–902. **DOI:**10.17344/acsi.2017.3506
11. M. Moghaddam-Manesh, D. Ghazanfari, E. Sheikhhosseini, M. Akhgar. *Acta Chim. Slov.***2020**, *67*, 7.

DOI:10.17344/acsi.2019.5437
12. F. Bossert, H. Meyer, E. Wehinger. *Angew. Chem. Int. Ed. Eng.* **1981**, *20*, 762–769. **DOI:**10.1002/anie.198107621
13. H. Andreas. *Mini-Rev. Med. Chem.* **2002**, *2*, 235–245. **DOI:**10.2174/1389557023406241
14. S. Cihat, S. Rahime. *Mini-Rev. Med. Chem.* **2006**, *6*, 747–755. **DOI:**10.2174/138955706777698606
15. A. Hilgeroth, M. Wiese, A. Billich. *J. Med. Chem.* **1999**, *42*, 4729–4732. **DOI:**10.1021/jm991115k
16. M. Kawase, A. Shah, H. Gaveriya, N. Motohashi, H. Sakagami, A. Varga, J. Molnár. *Bioorg. Med. Chem.* **2002**, *10*, 1051–1055. **DOI:**10.1016/S0968-0896(01)00363-7
17. D. Vo, W. C. Matowe, M. Ramesh, N. Iqbal, M. W. Wolowyk, S. E. Howlett, E. E. Knaus. *J. Med. Chem.* **1995**, *38*, 2851–2859. **DOI:**10.1021/jm00015a007
18. T. Naqvi, A. Amin, S. Ali, M. Y. Lone, N. Bashir, S. U. Khan, T. T. Htare, M. A. Rizvi. *Acta Chim. Slov.* **2021**, *68*, 16. **DOI:**10.17344/acsi.2021.6684
19. J. M. Tusell, S. Barro, N, J. Serratosa. *Brain Res.* **1993**, *622*, 99–104. **DOI:**10.1016/0006-8993(93)90807-Y
20. G. Sabitha, K. Arundhathi, K. Sudhakar, B. S. Sastry, J. S. Yadav. *Synth. Commun.* **2009**, *39*, 2843–2851. **DOI:**10.1080/00397910802656091
21. S.-J. Ji, Z.-Q. Jiang, J. Lu, T.-P. Loh. *Synlett* **2004**, *2004*, 0831–0835. **DOI:**10.1055/s-2004-820035
22. M. M. Heravi, M. Saeedi, N. Karimi, M. Zakeri, Y. S. Beheshtiha, A. Davoodnia. *Synth. Commun.* **2010**. *40*, 523–529. **DOI:**10.1080/00397910902994194
23. H. Salehi, Q. X. Guo. *Synth. Commun.* **2004**, *34*, 171–179. **DOI:**10.1081/SCC-120027250
24. S. Ghosh, F. Saikh, J. Das, A. K. Pramanik. *Tetrahedron Lett.* **2013**, *54*, 58–62. **DOI:**10.1016/j.tetlet.2012.10.079
25. G. Ali, N. A. Dangroo, S. Raheem, T. Naqvi, T. Ara, M. A. Rizvi. *Acta Chim. Slov.* **2020**, *67*, 195–202. **DOI:**10.17344/acsi.2019.5348
26. S. Behrouz, M. N. Abi, M. A. Piltan. *Acta Chim. Slov.* **2021**, *68*, 374–386. **DOI:**10.17344/acsi.2020.6343
27. J. E. Gholtash, M. Farahi, B. Karami, M. Abdollahi. *Acta Chim. Slov.* **2020**, *67*, 866–875. **DOI:**10.17344/acsi.2020.5825
28. M. Maheswara, V. Siddaiah, Y. K. Rao, Y.-M. Tzeng, C. Sridhar. *J. Mol. Catal. A: Chem.* **2006**, *260*, 179–180. **DOI:**10.1016/j.molcata.2006.07.024
29. M. Anniyappan, D. Muralidharan, P. T. Perumal. *Tetrahedron* **2002**, *58*, 5069–5073. **DOI:**10.1016/S0040-4020(02)00461-1
30. E. Rafiee, S. Eavani, S. Rashidzadeh, M. Joshaghani. *Inorg. Chim. Acta* **2009**, *362*, 3555–3562. **DOI:**10.1016/j.ica.2009.03.049
31. R. A. Mekheimer, A. A. Hameed, K. U. Sadek. *Green Chem.* **2008**, *10*, 592–593. **DOI:**10.1039/b715126h
32. S. Ko, M. N. V. Sastry, C. Lin, C.-F. Yao. *Tetrahedron Lett.* **2005**, *46*, 5771–5774. **DOI:**10.1016/j.tetlet.2005.05.148
33. R. Gupta, R. Gupta, S. Paul, A. Loupy. *Synthesis* **2007**, *2007*, 2835–2838. **DOI:**10.1055/s-2007-983839
34. M. A. Ghasemzadeh, S. M. Hasan Nasrollahi, M. R. Zolfaghari. *Acta Chim. Slov.* **2018**, *65*, 199–208. **DOI:**10.17344/acsi.2017.3820
35. A. Gharib, M. Jahangir, M. Roshani, J. W. Scheeren. *Synth. Commun.* **2012**, *42*, 3311–3320. **DOI:**10.1080/00397911.2011.581405
36. M. Adharvana Chari, K. Syamasundar. *Catal. Commun.* **2005**, *6*, 624–626. **DOI:**10.1016/j.catcom.2005.03.010
37. S. M. Baghbanian, S. Khaksar, S. M. Vahdat, M. Farhang, M. Tajbakhsh. *Chin. Chem. Lett.* **2010**, *21*, 563–567. **DOI:**10.1016/j.cclet.2009.12.011
38. S. Das Sharma, P. Hazarika, D. Konwar. *Catal. Commun.* **2008**, *9*, 709–714. **DOI:**10.1016/j.catcom.2007.08.008
39. L.-M. Wang, J. Sheng, L. Zhang, J.-W. Han, Z.-Y. Fan, H. Tian, C.-T. Qian. *Tetrahedron* **2005**, *61*, 1539–1543. **DOI:**10.1016/j.tet.2004.11.079
40. F.-P. Ma, P.-H. Li, B.-L. Li, L.-P. Mo, N. Liu, H.-J. Kang, Y.-N. Liu, Z.-H. Zhang. *Appl. Catal. A: General* **2013**, *457*, 34–41. **DOI:**10.1016/j.apcata.2013.03.005
41. A. Han, J. Liao, M. Ye, Y. Li, X. Peng. *Chin. J. Chem. Eng.* **2011**, *19*, 1047–1051. **DOI:**10.1016/S1004-9541(11)60090-6
42. J. Mondal, T. Sen, A. Bhaumik. *Dalton Trans.* **2012**, *41*, 6173–6181. **DOI:**10.1039/c2dt30106g
43. M. Hamidinasab, A. Mobinikhaledi. *ChemistrySelect* **2019**, *4*, 17–23. **DOI:**10.1002/slct.201802413
44. R. Karimi-Chayjani, N. Daneshvar, H. Tajik, F. Shirini. *ChemistrySelect* **2019**, *4*, 1205–1213. **DOI:**10.1002/slct.201802916
45. T. T. Nguyen, N. P. Thi Le, T. T. Nguyen, P. H. Tran. *RSC Adv.* **2019**, *9*, 38148–38153. **DOI:**10.1039/C9RA08074K
46. H. Alinezhad, K. Pakzad, M. Nasrollahzadeh. *Appl. Organomet. Chem.* **2020**, 34:e5473. **DOI:**10.1002/aoc.5473
47. M. A. Ashraf, Z. Liu, W. X. Peng, C. Gao. *Catal. Lett.* **2020**, *150*, 683–701. **DOI:**10.1007/s10562-019-02986-2
48. P. Lahiri, S. K. Sengupta. *Can. J. Chem.* **1991**, *69*, 33–36. **DOI:**10.1139/v91-006
49. J.-H. Lee, Y.-M. Huh, Y.-W. Jun, J.-W. Seo, J.-T. Jang, H.-T. Song, S. Kim, E.-J. Cho, H.-G. Yoon, J.-S. Suh, J. Cheon. *Nat. Med.* **2007**, *13*, 95–99. **DOI:**10.1038/nm1467
50. Z. Zarnegar, J. Safari. *Int. J. Biol. Macromol.* **2015**, *75*, 21–31. **DOI:**10.1016/j.ijbiomac.2015.01.013
51. B. Datta, M. A. Pasha. *Chin. J. Catal.* **2011**, *32*, 1180–1184. **DOI:**10.1016/S1872-2067(10)60252-5
52. E. Priede, A. Zicmanis. *Helv. Chim. Acta* **2015**, *98*, 1095–1103. **DOI:**10.1002/hlca.201500009
53. Y. Watanabe, K. Shiota, T. Hoshiko, S. Ozaki. *Synthesis* **1983**, *1983*, 761–761. **DOI:**10.1055/s-1983-30505
54. J. Safari, F. Azizi, M. Sadeghi. *New J. Chem.* **2015**, *39*, 1905–1909. **DOI:**10.1039/C4NJ01730G
55. M. José Climent, A. Corma, S. Iborra. *RSC Adv.* **2012**, *2*, 16–58. **DOI:**10.1039/C1RA00807B
56. M. Leonardi, M. Villacampa, J. C. Menéndez. *Chem. Sci.* **2018**, *9*, 2042–2064. **DOI:**10.1039/C7SC05370C
57. J.-P. Wan, Y. Liu. *RSC Adv.* **2012**, *2*, 9763–9777. **DOI:**10.1039/c2ra21406g

Povzetek

V prispevku je opisana učinkovita sinteza nekaterih 1,4-dihidropiridinov s pomočjo kondenzacijske reakcije aldehidov, etilacetoacetata in amonijevega acetata, v prisotnosti superparamagnetnih nanodelcev manganovega ferita pri 80 °C. Prednosti tega postopka so selektivnost, visoka čistost produktov, odlični izkoristki, kratki reakcijski časi, enostavna izolacija in okolju prijazni pogoji sinteze. Poleg tega je mogoče katalizator izolirati in večkrat ponovno uporabiti, ne da bi s tem bistveno zmanjšali izkoristek reakcije.