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RESEARCH PAPER

Cobalt Nanoparticles Promoted Highly Efficient One Pot Four-Component Synthesis of 1,4-Dihydropyridines under Solvent-Free Conditions

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Abstract: A straightforward and general method has been developed for the synthesis of C_5-unsubstitiuted 1,4-dihydropyridines by a reaction using dimedone, acetophenone, aromatic aldehydes, and ammonium acetate in the presence of a catalytic amount of Co nanoparticles as a heterogeneous and eco-friendly catalyst with high catalytic activity at room temperature under solvent-free conditions. This catalyst is easily separated by magnetic devices and can be reused without any apparent loss of activity for the reaction. In addition, it is very interesting that when using Co nanoparticles as a catalyst, spatially-hindered aldehydes such as 2-methoxy-, 2-fluoro-, and 2-chloro-aldehydes are suitable for this reaction.

Key words: cobalt nanoparticle; 1,4-dihydropyridine; four-component condensation; heterogeneous catalyst; magnetically separable catalyst

The efficiency of heterogeneous catalysis in organic synthesis can be improved by nanosized catalysts because of their extremely small size and their large surface to volume ratios [1]. Homogeneous systems have the advantage of high catalytic activity and selectivity, but the catalysts are difficult to separate from the products. To improve catalyst separation much effort has been devoted to organic reactions in heterogeneous mode [2,3]. Recently, it has been shown that Co nanoparticles (Co NPs), as catalysts, offer great opportunities for a wide range of applications in organic synthesis and in chemical manufacturing processes [4–9]. Green chemistry emphasizes the development of environmentally benign chemical processes and technologies [10]. Besides typical multi-step syntheses, an increasing number of organic chemical compounds are being produced by multicomponent reactions (MCRs). MCRs often comply with the principles of green chemistry in terms of the economy of steps as well as the many stringent criteria of ideal organic synthesis. MCRs offer great possibilities for molecular diversity per step with a minimum synthesis time, labor, cost, and waste production. As a one-pot reaction, MCRs generally afford good yields and are fundamentally different from two-component and stepwise reactions in several ways [11] and they permit rapid access to combinatorial libraries of complex organic molecules for an efficient lead structure identification and for optimization in drug discovery. 1,4-Dihydropyridines (1,4-DHPs) are an important class of compounds in the field of drugs and pharmaceuticals [12–16]. The DHP moiety is common to numerous bioactive compounds and these include various antihypertensives such as nifedipine, nicardipine and amlodipine, vasodilator, antimutagenic, antitumor, and antidiabetic agents [17–20]. These examples clearly demonstrate the remarkable potential of 1,4-DHPs derivatives as a source of valuable drugs. Despite the many methods available for the synthesis of dihydropyridine derivatives [21–35], their widespread use has accentuated the need to develop new synthetic routes for *N*-heterocycles containing the dihydropyridine moiety. Recent protocols have employed three-component condensations of dimedone, chal-

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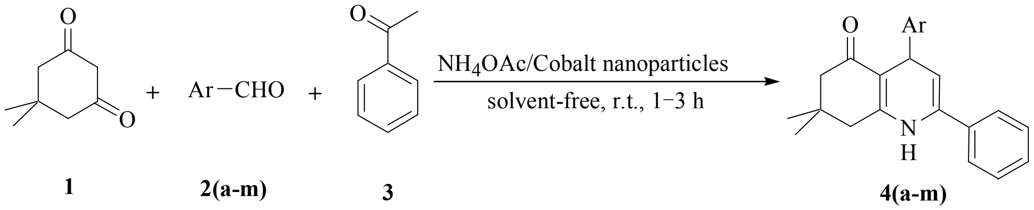

Scheme 1. Co NPs efficiently catalyzed synthesis of 1,4-DHPs.

cone derivatives, and ammonium acetate [36,37]. Synthetic methods should be designed to use substances that have little or no toxicity to human health and the environment. Therefore, the possibility of performing multicomponent reactions under solvent-free conditions with heterogeneous catalysts like Co NPs as a magnetically separable catalyst can enhance their efficiency from an economic as well as a green point of view. Thus, the remarkable catalytic activity and easy synthesis, operational simplicity, eco-friendliness, and recoverability of Co NPs encouraged us to use it as a catalyst for the synthesis of 1,4-DHPs [38]. To the best of our knowledge there are no examples of the use of Co NPs as catalysts for the four-component synthesis of C_5-unsubstitiuted 1,4-DHPs. In a continuation of our effort to develop new and green chemistry methods as well as our interest in applications of heterogeneous-catalyzed organic reactions [39] we explored the possibility of synthesizing pure metallic Co NPs and C_5-unsubstitiuted 1,4-DHPs by a one-pot and four-component reaction under solvent-free conditions using Co NPs as a recyclable and magnetically separable catalyst at room temperature, as shown in Scheme 1.

1 Experimental

1.1 General

All reagents were purchased from Merck and Aldrich and used without further purification. 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. ^{1}H 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. Elemental analyses (C, H, and N) were obtained using a Carlo ERBA Model EA 1108 analyzer and carried out on a Perkin-Elmer 240c analyzer. X-ray diffraction (XRD) patterns were recorded on an X-ray diffractometer (PAN analytical X'pert-pro) using a Cu K_α monochromatized radiation source and a Ni filter in a 2θ range of 30°–90°. BET surface area analyses were performed at –196 °C using an automated gas adsorption analyzer (Tristar 3000, Micromeritics). The composition and microstructure of the specimens were analyzed using a scanning electron microscope (SEM, JSM-5600LV) equipped with an energy-dispersion analytical X-ray spectroscope (EDS).

1.2 Catalyst preparation

A dark blue solution was formed after dissolving the cobalt salt ($CoCl_2\cdot 6H_2O$ or $CoSO_4\cdot 7H_2O$) in ethanol and then a mixture of hydrazine hydrate ($N_2H_4\cdot H_2O$) and sodium hydroxide (NaOH) was added to the dark blue solution at 200 °C. After about 30 min, gray solid particles appeared and reacted quickly. The suspended gray particles can be precipitated by placing a magnet under the container. After reaction completion the gray particles were washed with distilled water, ethanol, and absolute ethanol to remove hydrazine, sodium, and chlorine ions. The sample was then kept in absolute ethanol [40].

1.3 Synthesis of C_5-unsubstitiuted 1,4-DHPs

Dimedone (1 mmol) and an aromatic aldehyde (1 mmol) were added to a mixture of acetophenone (1 mmol), ammonium acetate (1 mmol), and Co NPs (10 mol%). The mixture was then stirred at room temperature. The reaction was completed within 1–2 h, as confirmed by TLC. The mixture was then extracted with ethyl acetate and the organic layer was dried over sodium sulphate and concentrated in a vacuum to afford the crude products. The Co NPs were recovered using a magnet and reused four times in the same reaction (Table 5).

4-(3,4-dimethoxyphenyl)-7,7-dimethyl-2-phenyl-4,6,7,8-tetrahydro-5(1H)-quinolinone (**4g**): mp 201–203 ºC; IR (KBr, cm^{-1}) 3341, 1674, 1729; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (s, 3H), 1.16 (s, 3H), 2.22–2.50 (m, 4H), 3.72 (s, 3H), 3.75 (s, 3H), 4.66 (d, J = 5.1 Hz, 1H), 5.22 (d, J = 5.1 Hz, 1H), 5.81 (s, 1H, NH), 6.82 (s, 1H), 7.0–7.30 (m, 5H), 7.34 (d, J = 8.1 Hz, 1H), 7.52 (d, J = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.9, 29.3, 32.5, 36.5, 42.5, 50.3, 57.5, 57,8, 107.4, 107.9, 111.5, 121.2, 125.8, 126.7, 128.4, 128.9, 129.1, 129.8, 135.1, 135.7, 148.4, 151.4, 196.8; Anal. Calcd. for $C_{25}H_{27}NO_3$: C, 77.09; H, 6.99; N, 3.60. Found: C, 76.98; H, 6.95; N, 3.58.

4-(3-Bromoyphenyl)-7,7-dimethyl-2-phenyl-4,6,7,8-tetrahydro-5(1H)-quinolinone (**4h**): mp 224–227 ºC; IR (KBr, cm^{-1}) 3340, 1668, 1733; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (s, 3H), 1.15 (s, 3H), 2.20–2.40 (m, 4H), 4.64 (d, J = 4.9 Hz, 1H), 5.27 (d, J = 4.9 Hz, 1H), 5.75 (s, 1H, NH), 7.0–7.30 (m, 5H), 7.32 (s, 1H), 7.38 (d, J = 7.5 Hz, 1H), 7.54 (d, J = 7.3 Hz, 1H), 7.69 (dd, J = 7.5 Hz, J = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$):