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 C₅-unsubstituted 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
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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 combina-

torial 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, chalcone 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

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

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 -unsubstituted 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 -unsubstituted 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. ^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. 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 $\text{Cu } K_\alpha$ 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 spectroscopy (EDS).

1.2 Catalyst preparation

A dark blue solution was formed after dissolving the co-

balt salt ($\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ or $\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$) in ethanol and then a mixture of hydrazine hydrate ($\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$) 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 -unsubstituted 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°C ; IR (KBr, cm^{-1}) 3341, 1674, 1729; ^1H 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 $\text{C}_{25}\text{H}_{27}\text{NO}_3$: C, 77.09; H, 6.99; N, 3.60. Found: C, 76.98; H, 6.95; N, 3.58.

4-(3-Bromophenyl)-7,7-dimethyl-2-phenyl-4,6,7,8-tetrahydro-5(1H)-quinolinone (**4h**): mp 224 – 227°C ; IR (KBr, cm^{-1}) 3340, 1668, 1733; ^1H 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): δ 26.8, 29.8, 33.1, 36.1,

41.2, 51.8, 106.9, 108.5, 110.4, 112.8, 125.1, 127.3, 128.4, 129.4, 129.5, 130.4, 135.7, 136.4, 149.1, 156.2, 196.3; Anal. Calcd. for $C_{23}H_{22}BrNO$: C, 67.65; H, 5.43; N, 3.43. Found: C, 67.49; H, 5.40; N, 3.39.

4-(3-chlorophenyl)-7,7-dimethyl-2-phenyl-4,6,7,8-tetrahydro-5(1H)-quinolinone (**4i**): mp 214–217 °C; IR (KBr, cm^{-1}) 3341, 1664, 1732; 1H NMR (400 MHz, $CDCl_3$): δ 1.16 (s, 3H), 1.17 (s, 3H), 2.22–2.45 (m, 4H), 4.55 (d, J = 4.8 Hz, 1H), 5.23 (d, J = 4.8 Hz, 1H), 5.72 (s, 1H, NH), 7.0–7.40 (m, 5H), 7.42 (s, 1H), 7.47 (d, J = 7.2 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.74 (dd, J = 7.8 Hz, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.1, 29.4, 33.7, 35.4, 42.5, 52.1, 107.5, 108.7, 111.1, 112.2, 125.5, 126.7, 128.8, 129.1, 130.5, 131.1, 134.1, 136.8, 150.8, 157.1, 197.4; Anal. Calcd. for $C_{23}H_{22}ClNO$: C, 75.92; H, 6.09; N, 3.85. Found: C, 75.90; H, 5.35; N, 3.35.

4-(4-bromophenyl)-7,7-dimethyl-2-phenyl-4,6,7,8-tetrahydro-5(1H)-quinolinone (**4j**): mp 217–220 °C; IR (KBr, cm^{-1}) 3344, 1679, 1731; 1H NMR (400 MHz, $CDCl_3$): δ 1.11 (s, 3H), 1.13 (s, 3H), 2.20–2.50 (m, 4H), 4.74 (d, J = 4.7 Hz, 1H), 5.34 (d, J = 4.7 Hz, 1H), 5.79 (s, 1H, NH), 7.0–7.25 (m, 5H), 7.36 (d, J = 7.9 Hz, 2H), 7.45 (d, J = 7.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.4, 29.4, 32.7, 37.9, 41.9, 50.7, 107.1, 108.3, 125.2, 126.1, 127.9, 128.3, 128.7, 128.8, 134.2, 135.8, 147.7, 151.0, 195.5; Anal. Calcd. for $C_{23}H_{22}BrNO$: C, 67.65; H, 5.43; N, 3.43. Found: C, 67.49; H, 5.40; N, 3.39.

4-(2-fluorophenyl)-7,7-dimethyl-2-phenyl-4,6,7,8-tetrahydro-5(1H)-quinolinone (**4k**): mp 198–200 °C; IR (KBr, cm^{-1}) 3337, 1672, 1750; 1H NMR (400 MHz, $CDCl_3$): δ 1.08 (s, 3H), 1.12 (s, 3H), 2.25–2.57 (m, 4H), 4.68 (d, J = 4.8 Hz, 1H), 5.29 (d, J = 4.8 Hz, 1H), 5.67 (s, 1H, NH), 6.95 (dd, J = 9.2 Hz, J = 8.4 Hz, 1H), 7.21 (dd, J = 7.6 Hz, J = 7.2 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 7.42 (dd, J = 8.4 Hz, J = 7.2 Hz, 1H), 7.6–7.90 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.4, 29.4, 32.7, 37.9, 41.9, 50.7 (d, J = 9.2 Hz), 107.1, 108.3, 116.7 (d, J = 21.4 Hz), 125.2, 126.1, 127.9, 127.9 (d, J = 21.7 Hz), 128.3, 129.7 (d, J = 7.9 Hz), 128.8, 134.2, 135.8, 147.7, 161.0 (d, J = 249 Hz), 195.5; Anal. Calcd. for $C_{23}H_{22}FNO$: C, 69.51; H, 6.38; N, 4.03. Found: C, 69.46; H, 5.38; N, 3.35.

4-(4-fluorophenyl)-7,7-dimethyl-2-phenyl-4,6,7,8-tetrahydro-5(1H)-quinolinone (**4l**): mp 210–213 °C; IR (KBr, cm^{-1}) 3339, 1676, 1735; 1H NMR (400 MHz, $CDCl_3$): δ 1.15 (s, 3H), 1.17 (s, 3H), 2.29–2.40 (m, 4H), 4.56 (d, J = 5.1 Hz, 1H), 5.02 (d, J = 5.1 Hz, 1H), 6.13 (s, 1H, NH), 6.80 (dd, J = 8.9 Hz, J = 7.4 Hz, 2H), 7.31 (dd, J = 8.9 Hz, J = 4.2 Hz, 2H), 7.6–8.55 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.8, 29.9, 32.2, 36.2, 42.4, 49.9, 107.4, 108.8, 123.2 (d, J = 22 Hz), 126.1, 127.9, 128.3 (d, J = 8 Hz), 129.7, 138.8, 139.2, 140.8, 150.6, 163.5 (d, J = 244 Hz), 194.5; Anal. Calcd. for $C_{23}H_{22}FNO$: C, 69.51; H, 6.38; N, 4.03. Found:

C, 69.46; H, 5.38; N, 3.35.

4-(2-methoxyphenyl)-7,7-dimethyl-2-phenyl-4,6,7,8-tetrahydro-5(1H)-quinolinone (**4m**): mp 196–199 °C; IR (KBr, cm^{-1}) 3343, 1666, 1745; 1H NMR (400 MHz, $CDCl_3$): δ 1.13 (s, 3H), 1.19 (s, 3H), 2.21–2.40 (m, 4H), 4.67 (d, J = 4.4 Hz, 1H), 5.62 (d, J = 4.4 Hz, 1H), 5.58 (s, 1H, NH), 7.06 (d, J = 8.1 Hz, 1H), 7.11 (dd, J = 7.9 Hz, J = 7.3 Hz, 1H), 7.14 (d, J = 7.3 Hz, 1H), 7.27 (dd, J = 8.1 Hz, J = 7.9 Hz, 1H), 7.36–7.50 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.4, 29.4, 32.7, 37.9, 41.9, 50.7, 57.4, 108.3, 110.6, 122.7, 125.3, 125.9, 126.4, 126.8, 127.3, 128.2, 131.6, 132.7, 138.3, 140.2, 197.9; Anal. Calcd. for $C_{24}H_{25}NO_2$: C, 80.19; H, 7.01; N, 3.90. Found: C, 80.07; H, 6.98; N, 3.86.

2 Results and discussion

We had the opportunity to further explore the catalytic activity of Co NPs for the synthesis of 1,4-DHPs. The crystallite size of the Co NPs was determined by XRD and the results are presented in Fig. 1(a). The XRD peaks were FCC (111), (200), and (220) for the sample synthesized at 200 °C in an ethanol hydrazine alkaline system and were assigned using JCPDS 15-806 for the cubic lattice. An examination of the sample by SEM (Fig. 1(b)) reveals that the diameters of the nanoparticles are less than 90 nm, which agrees with the size calculated from the XRD pattern using the Scherrer equation.

The lattice parameter of the prepared Co NPs was 0.204

Fig. 1. XRD pattern (a) and SEM image (b) of the prepared Co NPs in ethanol hydrazine alkaline system.

nm, which is in good agreement with JCPDS 15-806. The crystallite sizes were 83.2, 78.8, and 77.4 nm, respectively, calculated on the (111), (200), and (220) diffraction maxima from the half-width of the diffraction peak using Scherrer formula.

In addition the surface area was found to be approximately 95 cm²/g. The pore volume and pore size were also calculated from the N₂ adsorption result. The pore size was found to be approximately 46.17 nm and the pore volume approximately 1.55 cm³/g. The theoretical particle size was also calculated from the surface area, assuming spherical particles, from the equation $D_{\text{BET}} = 6000/(\rho \times S)$, where D_{BET} is the equivalent particle diameter in nm, ρ is the density of the material in g/cm³ and S is the specific surface area in m²/g. The particle size calculated from the equation was 87.93 nm, which confirmed the nanostructure of the Co NPs sample. The difference between the particle morphology and the size distribution that was obtained at different temperatures and at different Co²⁺ concentrations can be explained by the reaction rate of nucleation [40].

Subsequent efforts focused on optimizing the concentration of the catalyst Co NPs and we investigated the model reaction between dimedone, benzaldehyde, acetophenone, and ammonium acetate at different concentrations of Co NPs such as 2 mol%, 4 mol%, 6 mol%, 8 mol%, 10 mol%, and 12 mol%. Products were obtained in 35%, 45%, 60%, 75%, 98%, and 90% yields, respectively. This indicates that 10 mol% of Co NPs produced the best results with respect to the product yield (Table 1).

Table 1 Optimizing the reaction conditions

Entry	Co NPs (mol%)	Time (h)	Isolated yield (%)
1	0	6.0	30
2	2	3.0	35
3	4	3.0	45
4	6	3.0	60
5	8	3.0	75
6	10	1.0	98
7	10 ^a	6.0	50
8	12	3.0	90

Reaction conditions: dimedone:benzaldehyde:acetophenone:ammonium acetate = 1:1:1:1. ^aUsing commercial cobalt powder.

We then continued to optimize the model process mentioned above by determining the efficiency of several classic solvents that were chosen as a medium for comparison. In each case, the substrates were mixed with 10 mol% Co NPs and agitated with 3–5 ml of solvent. Among the tested solvents such as methanol, ethanol, acetonitrile, dichloromethane, water, and a solvent-free system, the formation of product **4a** was found to be more facile and proceeded to give the highest yield only under solvent-free reaction conditions (Table 2).

Table 2 Solvent screening for the reaction between dimedone, benzaldehyde, acetophenone, and ammonium acetate

Entry	Solvent	Time (h)	Isolated yield (%)
1	EtOH	6.0	60
2	MeOH	6.0	50
3	acetonitrile	6.0	30
4	dichloromethane	24.0	trace
5	water	6.0	80
6	none	1.0	98

Reaction conditions: Co NPs (10% mol), dimedone:benzaldehyde:acetophenone:ammonium acetate = 1:1:1:1.

A possible explanation for the higher yield under solvent-free conditions is that the eutectic mixture has a uniform distribution of reactants and the reacting species are in closer proximity for the reaction compared with that in a solvent. The environment of the reaction system in the absence of a solvent is different from that in solution resulting in a higher concentration of local reaction sites and an improved global efficiency. To further expand the scope of this method the replacement of Co NPs by commercial cobalt powder was examined. We carried out a reaction between dimedone (**1**), benzaldehyde (**2a**), acetophenone (**3**), and ammonium acetate using the commercial cobalt powder (10 mol%) under solvent-free conditions at room temperature. When the reaction was carried out using the commercial cobalt powder, 50% of product **4a** was obtained in 6 h. The catalytic activity of the Co NPs was evident when only 30% and 50% product was obtained in the absence of the catalyst and when using the commercial cobalt powder, respectively (Table 1, entries 1 and 7). The high efficiency of the metal nanoparticles is caused by their high surface area and 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 constituent atoms have highly defective coordination environments. These properties of the Co NPs gave spatially-hindered aldehydes such as 2-methoxy-, 2-fluoro-, and 2-chloro-aldehydes, which function well in this reaction (Table 3). The Co NPs also act as a mild Lewis acid and catalyze the four-component, one-pot synthesis of C₅-unsubstituted 1,4-DHPs.

An investigation into the reaction scope revealed that various aromatic aldehydes (bearing electron-withdrawing and electron-donating groups) can be used in this protocol (Table 3). The nature of the substituent on the aromatic ring had no obvious effect on this conversion because high yields were obtained over relatively short reaction times. The structures of the isolated products **4a–4m** were determined by IR, ¹H NMR and ¹³C NMR spectroscopy, and elemental analysis.

After successfully synthesizing a series of polyhydroquinolines in excellent yields, we used β -ketoesters to show the validity of this methodology. We thus carried out a

Table 3 Co NPs catalyzed unsymmetrical one-pot four-component synthesis of 1,4-DHPs

Product	Ar	Time (h)	Isolated yield (%)	Melting point (°C)	
				Found	Reported
4a	C ₆ H ₅	1.0	98	203–205	206–208 [36]
4b	4-ClC ₆ H ₄	1.5	90	222–224	224–226 [36]
4c	2,4-Cl ₂ C ₆ H ₃	2.5, 6.0 ^a	80, 45 ^a	206–208	204–206 [36]
4d	4-NO ₂ C ₆ H ₄	1.5	90	211–213	212–214 [37]
4e	4-CH ₃ C ₆ H ₄	1.0	95	184–186	186–188 [37]
4f	4-MeOC ₆ H ₄	1.0	92	190–192	192–194 [37]
4g	3,4-MeOC ₆ H ₃	1.5	88	201–203	—
4h	3-BrC ₆ H ₄	1.5	94	224–227	—
4i	3-ClC ₆ H ₄	1.5	92	214–216	—
4j	4-BrC ₆ H ₄	1.5	92	217–220	—
4k	2-FC ₆ H ₄	2.0, 6.0 ^a	75, 40 ^a	198–201	—
4l	4-FC ₆ H ₄	1.0	95	210–213	—
4m	2-MeOC ₆ H ₄	3.0, 6.0 ^a	65, 30 ^a	196–199	—

Reaction conditions: Co NPs (10% mol), dimedone:benzaldehyde:acetophenone:ammonium acetate = 1:1:1:1.

^aUsing commercial cobalt powder.

four-component coupling reaction among dimedone, some aromatic aldehydes, alkyl acetoacetate, and ammonium acetate under the same reaction conditions.

The structural variation of the β -ketoesters did not obviously affect this conversion because the desired products were obtained in high yields and in relatively short reaction time (Table 4).

We examined the recovery and reuse of the catalyst. The catalyst was recovered using magnetic decantation and re-used in four consecutive runs without any apparent loss of activity for the same reaction. The yield of the product in the second, third, and fourth runs was almost the same as that in the first run, as shown in Table 5.

Figure 2 shows EDAX patterns of the fresh and the 2nd recycle nanoparticles. Interestingly, the total composition of

cobalt was found in the resultant sample. However, EDAX results show that the catalyst consists mainly of cobalt (98%), and a small amount of oxygen is also present while no other elements were found using EDAX. The oxygen detected by EDAX might come from oxides such as CoO or

Table 5 Reuse of Co NPs in the synthesis of 1,4-DHPs

Run	Isolated yield (%)
Fresh	98
1	97
2	97
3	95
4	94

Reaction conditions: Co NPs (10% mol), dimedone:benzaldehyde:acetophenone:ammonium acetate = 1:1:1:1.

Table 4 Co NPs catalyzed unsymmetrical one-pot four-component synthesis of 1,4-DHPs with different β -keto compounds

Product	R	Ar	Time (h)	Isolated yield (%)	Melting point (°C)	
					Found	Reported
5a	Et	C ₆ H ₅	1.0	95	203–204	202–203 [28]
5b	Et	2-ClC ₆ H ₄	2.0	85	207–210	208–210 [28]
5c	Et	4-MeC ₆ H ₄	1.5	90	259–261	260–261 [28]
5d	Et	2-thienyl	1.0	92	237–239	238–240 [28]
5e	Et	4-OMeC ₆ H ₄	1.5	93	258–260	257–259 [28]
5f	Et	3-BrC ₆ H ₄	1.0	90	234–237	235–236 [28]
5g	Me	2-thienyl	1.5	90	216–218	216–217 [29]
5h	Me	4-ClC ₆ H ₄	1.0	95	221–222	222–223 [29]
5i	Me	4-MeC ₆ H ₄	1.2	88	283–285	>280 [31]
5j	Me	C ₆ H ₅	1.0	90	258–260	260–261 [35]
5k	Me	3,4,5-OMeC ₆ H ₂	2.0	85	285–287	>270 [30]

Reaction conditions: Co NPs (10% mol), dimedone:benzaldehyde: β -ketoesters:ammonium acetate = 1:1:1:1.

Fig. 2. EDAX patterns of fresh (1) and 2nd recycle (2) Co NPs.

Co₃O₄, as a result of the oxidation of cobalt during the reaction and after treatment.

3 Conclusions

A four-component reaction between dimedone, aromatic aldehydes, acetophenone, and ammonium acetate is shown to provide a simple synthetic route to C₅-unsubstituted 1,4-dihydropyridines using Co nanoparticles. We demonstrate for the first time that Co, in the form of nanoparticles, is a potential alternative to noble-metal-based catalysts for the unsymmetrical Hantzsch condensation. The mildness of the conversion, experimental simplicity, compatibility with various functional groups, excellent yields, shorter reaction time, and easy work-up make this procedure attractive for the synthesis of a variety of these derivatives. Because this heterogeneous catalyst can be simply removed using an external magnetic device, it also enhances product purity and is economic.

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