

## A mild protocol for the preparation of 2-amino-dihydropyrano[3,2-b] pyran-3-carbonitriles via cobalt nanoparticles-catalyzed multi-component reaction in water

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### Abstract

An improved rapid one-pot and green synthesis of substituted pyranopyranes by condensing Kojic acid, malononitrile, and different aldehydes using a catalytic amount of cobalt nanoparticles as a green and reusable catalyst is reported for the first time. The reaction proceeds in aqueous media at ambient temperature. Furthermore, the structural and morphological study of the cobalt nanoparticles was carried out using scanning electron microscopy (SEM), energy dispersive X-ray spectrum (EDS), and Dynamic light scattering (DLS) techniques. Utilization of simple procedure, high yields and the ease of separation of pure product, ease of catalyst separation by an external magnet and convenient manipulation make this methodology an interesting option for green synthesis of 2-amino-dihydropyrano[3,2-b]pyran-3-carbonitriles.

**Keywords:** 2-Amino-dihydropyrano[3,2-b]pyran-3-carbonitriles; cobalt nanoparticles; heterogeneous conditions; multi-component reaction; aqueous media.

### Introduction

Newly, catalysis researchers have focused their attentions towards greener and environmentally benign procedures which help prevent the use of toxic organic solvents, volatile reagents, harsh reaction conditions, and time-consuming processes [1-3]. Nanocatalysis has more advantages in catalyst science than conventional catalyst systems or bulk materials, such as high surface-to-volume ratio, easy separation process, low catalyst loading, and reusability of catalyst [4]. The use of magnetic separable nanocatalysts has a promising and adaptable role in research due to their insoluble and paramagnetic nature as it

enables easy separation of the catalysts from the reaction medium using an external magnet [5-9].

Green chemistry uses mild and highly efficient synthetic routes to deliver life-saving medicines, accelerating and guide optimization processes in drug discovery with reduced environmental impact [10]. In this regard the use of water as a promising solvent for organic reaction shows both economical and synthetic advantages such as an inexpensive, green, noncorrosive and non-volatile solvent. Furthermore, separation of organic compounds, which are insoluble in water from the aqueous phase, could easily be achieved.

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Moreover, the hydrophobic effects of water are not only causing the rapid progress of the reaction, but also high selectivity of reactants, it is so even when the reactants are sparingly soluble or insoluble in this medium [11].

Nowadays, multi-component reactions (MCRs) have been providing a versatile and practical approach for the synthesis of different structures of heterocyclic compounds [12-13]. MCRs are the processes that prevail the conversion of various starting materials in one-pot to a product with high diversity, complexity, and impressive selectivity. Therefore, these reactions are highly efficient, eco-friendly, and synthetically proficient in connection with decreasing the time, the number of reaction steps, the consumption of starting materials and hazardous chemical solvents [14-17].

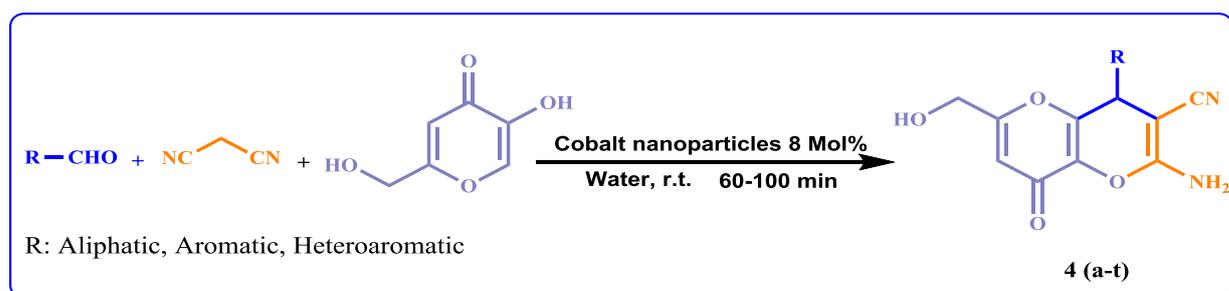
Multi-heterocyclic compounds have shown a wide spectrum of biological activities for the access of pharmaceutical and important scaffolds such as Kojic acid and fused-pyran which may lead to new alternative drug candidates with enhanced medicinal products [18]. It is significant to note that potential medicinal properties and high reactivity of Kojic acid make it an interesting molecule in pharmaceutical chemistry [19, 20]. Therefore, there are great efforts to provide practical and green procedures for the synthesis of fused-Kojic acid heterocycles [21-25].

Nowadays, recent researches are not only focusing on the development of simple and greener routes for the

synthesis of nanoparticles but also are focusing on the applications in organic synthesis and other fields. Magnetic nanoparticles show good catalytic activity in catalytic processes because of high surface area, high mechanical stability, increasing contacts between catalyst and reactants, and good dispersion in the reaction mixture. The magnetic separable nanoparticles are insoluble in the reaction medium, paramagnetic nature, and easy separation of nanocatalyst using a magnet which avoids the catalyst filtration; it prevents the aggregation of nanocatalyst which increases the recycling of the catalysts [28].

As a part of our research program on the development of MCRs in a greener way [29-30], and the continuation of previous research to develop application of cobalt nanoparticles as a catalyst in multi-component reaction [31], we wish to report a green and convenient protocol for the synthesis of 2-amino-dihydropyrano[3,2-b]pyran-3-carbonitriles *via* multi-component reaction of Kojic acid, aldehydes, malononitrile, over cobalt nanoparticles as catalysts under heterogeneous and aqueous media (Scheme 1).

The aim of this protocol is to highlight the assistant effects of the joint use of three-component reactions in aqueous media and application of nano metal catalyst with natural magnetic property for the development of new eco-friendly strategy for heterocyclic synthesis.



**Scheme 1.** Co NPs catalyzed synthesis of 2-amino-dihydropyrano[3,2-b]pyran-3-carbonitriles

## Experimental

### Materials and methods

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.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded with a Bruker DRX-400 spectrometer at 400 and 100 MHz, respectively. NMR spectra were obtained in  $\text{DMSO-d}_6$  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. The particle size distribution of the powder was measured by Dynamic Light Scattering in  $\lambda = 635$  nm using a Brookhaven 90 Plus/BI-MAS nanoparticle size analyzer. The composition and microstructure of the specimens were analyzed using a scanning electron microscope (SEM, JSM-5600LV) equipped analytical X-ray spectroscopy (EDS).

### General procedure for the preparation of Co NPs

According to the previously reported method [31], the cobalt salt ( $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$  or  $\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$ ) was dissolved 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) were added

to the dark blue ethanolic solution at  $200^\circ\text{C}$ . After about 30 min, gray solid particles appeared and reacted quickly. The suspended gray particles were precipitated by placing a magnet under the container. After completion of the reaction the gray particles were washed with distilled water, and absolute ethanol to remove hydrazine, sodium, and chlorine ions. The Co NPs were kept in absolute ethanol.

### Typical procedure for the synthesis of 2-amino-dihydropyrano[3,2-b]pyran-3-carbonitrile

A mixture of benzaldehyde (1.0 mmol, 1.06 g), kojic acid (1.0 mmol, 1.42 g), malononitrile (1.0 mmol, 0.07 g) and Co NPs (8 mol %, 0.015 g) were stirred at room temperature in 5 ml of water for a special time (Table 2). After complete conversion, as indicated by TLC (eluent: *n*-hexane–ethyl acetate, 4:1), the reaction mixture was diluted with acetone and the catalyst was removed from the reaction mixture using a magnet. The residue was concentrated in vacuum and crystallized in ethanol to afford pure products 4a-t. For the synthesis of the of product **5a**, a mixture of the terephthalaldehyde (1 mmol), kojic acid (2.0 mmol), malononitrile (2.0 mmol) and Co NPs (8 mol%) was stirred at room temperature in 5 ml of water for appropriate time (monitored by TLC, eluent: *n*-hexane–ethyl acetate, 3:1).

The workup was performed as mentioned above to give the pure product.

**2-Amino-4-(2,3-dimethoxyphenyl)-6-(hydroxymethyl)-8-oxo-4,8-dihydropyrano[3,2-b]pyran-3-carbonitrile (4n)**

Mp= 253-256 °C; IR (KBr): 3434 and 3320 (NH<sub>2</sub>), 3442 (OH), 2116 (CN), 1640 (C=O), 1110 (C-O) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ= 3.76 (s, 3H, OCH<sub>3</sub>), 3.81 (s, 3H, OCH<sub>3</sub>), 4.15 (dd, 1H, <sup>2</sup>J= 15.1, <sup>4</sup>J= 4.8 Hz, CH<sub>aliph</sub>), 4.20 (dd, 1H, <sup>2</sup>J= 15.1, <sup>4</sup>J= 4.8 Hz, CH<sub>aliph</sub>), 5.71 (t, 1H, <sup>4</sup>J= 4.8 Hz, OH), 5.71 (s, 1H, CH<sub>vinyl</sub>), 6.35 (dd, 1H, <sup>3</sup>J= 8.6, <sup>4</sup>J= 2.3 Hz, CH<sub>arom</sub>), 6.42 (s, 1H, CH<sub>aliph</sub>), 6.47 (dd, 1H, <sup>3</sup>J= 8.3, <sup>4</sup>J= 2.3 Hz, CH<sub>arom</sub>), 8.81 (dd, <sup>3</sup>J= 8.6, <sup>3</sup>J= 8.3 Hz, CH<sub>arom</sub>), 7.23 (s, 2H, NH<sub>2</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ<sub>c</sub>= 55.1, 55.4, 59.4, 98.1, 106.8, 112.3, 119.7, 135.3, 144.3, 148.7, 159.1, 161.2, 168.8, 169.2, 195.2 ppm., Anal. Calcd. For: C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>O<sub>6</sub>: C, 60.67; H, 4.53; N, 7.86; found: C, 60.64; H, 4.48; N, 7.83.

**2-Amino-4-(3,4-dihydroxyphenyl)-6-(hydroxymethyl)-8-oxo-4,8-dihydropyrano[3,2-b]pyran-3-carbonitrile (4o)**

Mp= 218-221 °C; IR (KBr): 3362 and 3321 (NH<sub>2</sub>), 3349 (OH), 2219 (CN), 1617 (C=O) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ= 4.22 (dd, 1H, <sup>2</sup>J= 15.1, <sup>4</sup>J= 6.2 Hz, CH<sub>aliph</sub>), 4.32 (dd, 1H, <sup>2</sup>J= 15.1, <sup>4</sup>J= 6.02 Hz, CH<sub>aliph</sub>), 5.33 (t, 1H, <sup>4</sup>J= 6.2 Hz, OH), 5.63 (s, 1H, CH<sub>vinyl</sub>), 6.44 (s, 1H, CH<sub>aliph</sub>), 6.51 (s, 1H, CH<sub>arom</sub>), 6.63 (d, 1H, <sup>2</sup>J= 7.9 Hz, CH<sub>arom</sub>), 6.85 (d, 1H, <sup>2</sup>J= 7.9 Hz, CH<sub>arom</sub>), 7.14 (s, 2H, NH<sub>2</sub>), p.88 (s, 1H, OH), 9.91 (s, 1H, OH), ppm; <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ<sub>c</sub>= 54.6, 59.0, 111.4, 118.9, 128.1, 129.7, 130.1, 130.8, 132.2, 136.9, 137.4, 147.9, 159.4, 168.2, 169.5, 194.9 ppm., Anal. Calcd. For: C<sub>16</sub>H<sub>12</sub>N<sub>2</sub>O<sub>6</sub>: C, 58.54; H,

3.68; N, 8.53; found: C, 58.50; H, 3.64; N, 8.51.

**(E)-2-amino-6-(hydroxymethyl)-8-oxo-4-styryl-4,8-dihydropyrano[3,2-b]pyran-3-carbonitrile (4p)**

Mp= 122-125 °C; IR (KBr): 3355 and 3359 (NH<sub>2</sub>), 3339 (OH), 2225 (CN), 1620 (C=O), 1604 (C=C) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ= 4.09 (dd, 1H, <sup>2</sup>J= 14.8, <sup>4</sup>J= 6.3 Hz, CH<sub>aliph</sub>), 4.33 (dd, 1H, <sup>2</sup>J= 14.8, <sup>4</sup>J= 6.3 Hz, CH<sub>aliph</sub>), 5.23 (t, 1H, <sup>4</sup>J= 6.3 Hz, OH), 5.55 (s, 1H, CH<sub>vinyl</sub>), 6.26 (s, 1H, CH<sub>aliph</sub>), 6.77 (d, <sup>3</sup>J=12.9 Hz, CH<sub>vinyl</sub>), 6.97 (d, <sup>3</sup>J=12.9 Hz, CH<sub>vinyl</sub>), 7.09 (s, 2H, NH<sub>2</sub>), 7.22-7.50 (m, 5H, CH<sub>arom</sub>) ppm; <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ<sub>c</sub>= 46.3, 57.6, 113.1, 117.3, 117.1, 129.5, 131.2, 132.5, 135.7, 138.1, 148.5, 159.6, 169.3, 169.5, 195.5 ppm., Anal. Calcd. For: C<sub>18</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>: C, 67.08; H, 4.38; N, 8.69; found: C, 67.02; H, 4.33; N, 8.65.

**2-Amino-6-(hydroxymethyl)-4-(5-methylfuran-2-yl)-8-oxo-4,8-dihydropyrano[3,2-b]pyran-3-carbonitrile (4q)**

Mp= 243-245 °C; IR (KBr): 3332 and 3171 (NH<sub>2</sub>), 33684 (OH), 2199 (CN), 1634 (C=O) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ= 2.35 (s, 3H, CH<sub>3</sub>), 4.23 (dd, 1H, <sup>2</sup>J= 14.3, <sup>4</sup>J= 6.1 Hz, CH<sub>aliph</sub>), 4.34 (dd, 1H, <sup>2</sup>J= 14.3, <sup>4</sup>J= 6.1 Hz, CH<sub>aliph</sub>), 5.15 (t, 1H, <sup>4</sup>J= 6.1 Hz, OH), 5.21 (s, 1H, CH<sub>vinyl</sub>), 6.35 (s, 1H, CH<sub>aliph</sub>), 7.28 (s, 2H, NH<sub>2</sub>), 7.46 (d, 1H, <sup>3</sup>J= 4.1, CH<sub>arom</sub>), 7.55 (d, 1H, <sup>3</sup>J= 4.1, CH<sub>arom</sub>) ppm; <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ<sub>c</sub>= 33.4, 55.3, 59.1, 106.5, 110.6, 111.9, 112.6, 119.4, 142.5, 142.1, 152.2, 159.4, 168.7, 196.6 ppm., Anal. Calcd. For: C<sub>15</sub>H<sub>12</sub>N<sub>2</sub>O<sub>5</sub>: C, 60.00; H, 4.03; N, 9.33; found: C, 59.94; H, 4.00; N, 9.29.

**2-Amino-4-ethyl-6-(hydroxymethyl)-8-oxo-4,8-dihydropyrano[3,2-b]pyran-3-carbonitrile (4r)**

Mp= 156-158 °C; IR (KBr): 3356 and 3345 (NH<sub>2</sub>), 3335 (OH), 2230 (CN), 1643 (C=O) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ= 1.12 (t, 3H, <sup>3</sup>J= 8.1 Hz, CH<sub>3</sub>), 1.52 (m, 2H, CH<sub>2</sub>), 4.13 (dd, 1H, <sup>2</sup>J= 14.5, <sup>4</sup>J= 6.0 Hz, CH<sub>aliph</sub>), 4.19 (dd, 1H, <sup>2</sup>J= 14.5, <sup>4</sup>J= 6.0 Hz, CH<sub>aliph</sub>), 5.27 (t, 1H, <sup>4</sup>J= 6.0 Hz, OH), 5.45 (s, 1H, CH<sub>vinyl</sub>), 6.29 (t, 1H, <sup>3</sup>J= 11.4 Hz, CH<sub>aliph</sub>), 7.19 (s, 2H, NH<sub>2</sub>) ppm; <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ<sub>c</sub>= 13.5, 17.3, 45.3, 58.6, 111.2, 117.9, 118.2, 128.5, 132.2, 136.5, 147.9, 158.3, 169.2, 194.2 ppm., Anal. Calcd. For: C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O<sub>4</sub>: C, 58.06; H, 4.87; N, 11.29; found: C, 57.98; H, 4.83; N, 11.23.

**2-Amino-4-butyl-6-(hydroxymethyl)-8-oxo-4,8-dihydropyrano[3,2-b]pyran-3-carbonitrile (4t)**

Mp= 167-169 °C; IR (KBr): 3366 and 3355 (NH<sub>2</sub>), 3344 (OH), 2223 (CN), 1632 (C=O) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ= 0.92 (t, 3H, <sup>3</sup>J= 7.8 Hz, CH<sub>3</sub>), 1.32 (m, 2H, CH<sub>2</sub>), 1.48 (m, 2H, CH<sub>2</sub>), 1.52 (m, 2H, CH<sub>2</sub>), 4.18 (dd, 1H, <sup>2</sup>J= 15.4, <sup>4</sup>J= 6.2 Hz, CH<sub>aliph</sub>), 4.31 (dd, 1H, <sup>2</sup>J= 15.4, <sup>4</sup>J= 6.2 Hz, CH<sub>aliph</sub>), 5.34 (t, 1H, <sup>4</sup>J= 6.2 Hz, OH), 5.35 (s, 1H, CH<sub>vinyl</sub>), 6.25 (t, 1H, <sup>3</sup>J= 15.4 Hz, CH<sub>aliph</sub>), 7.14 (s, 2H, NH<sub>2</sub>) ppm; <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ<sub>c</sub>= 12.1, 12.5, 13.1, 13.4, 16.9, 46.3, 57.9, 114.2, 116.9, 119.5, 127.9, 132.8, 135.9, 148.5, 159.9, 170.2, 198.5 ppm., Anal. Calcd. For: C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>: C, 60.86; H, 5.84; N, 10.14; found: C, 60.79; H, 5.80; N, 10.12.

**Results and discussion**

Multicomponent reactions are very powerful tools for the efficient synthesis of diverse, complex molecules *via* a green approach. One of the strategies to develop a greener methodology for the synthesis of pyrano-fused heterocyclic scaffolds is to perform the reaction under heterogeneous conditions along with green solvent.

In an initial endeavor, the reaction of kojic acid **1** (1 mmol), malononitrile **2** (1 mmol) and benzaldehyde **3** (1 mmol) was performed at various conditions as a model reaction (Table 1).

To start with, the model reaction was performed at ambient temperature which gave the desired product in 30% yield taking around 6 h (Entry 1). Further to this, in order to reduce the reaction time and also to increase the yield, the same reaction was carried out in the presence of different catalytic amounts of Co NPs under similar conditions. As expected, significant improvement was observed and the yield of **4a** was slightly increased to 40% using 2 mole% of catalyst; the mixture was stirred for only 3 h (Table 1, Entry 2). An increase in the quantity of Co NPs from 2 mol% to 8 mol% not only decreased the reaction time from 3 h to 1 h, but also increased the product yield from 40% to 90% (Table 1, Entries 2-5). Interestingly, we investigated the role and effect of Co NPs amounts in this reaction.

**Table 1.** Screening of various conditions for the synthesis of compound **4a**<sup>a</sup>

Entry	Co NPs (mol%)	Solvent (mL)	Time (h)	Yield (%) <sup>b</sup>
1	-	H <sub>2</sub> O	6	30
2	2	H <sub>2</sub> O	3	40
3	4	H <sub>2</sub> O	3	55
4	6	H <sub>2</sub> O	3	65
5	8	H <sub>2</sub> O	1	90
6	10	H <sub>2</sub> O	3	85
7	8 <sup>c</sup>	H <sub>2</sub> O	6	70
8	8	Toluene	6	65
9	8	CH <sub>3</sub> CN	6	45
10	8	C <sub>2</sub> H <sub>5</sub> OH	6	50

<sup>a</sup>Reaction conditions: various solvents (5 mL) at room temperature<sup>b</sup>Isolated yields<sup>c</sup>Using commercial cobalt powder (20 μm)

The use of higher amounts of catalyst (10 mol%) did not improve the result to an appreciable extent (Table 1, Entries 6). In order to examine the efficiency of Co NPs, model reaction was carried out in the presence of commercial cobalt powder in same conditions (Table 1, Entry 7). The results showed that only 70% of product **4a** was obtained after 6 hours. The catalytic activity of Co NPs was obvious when only 30 and 70% of product were obtained in the absence of catalyst using commercial cobalt powder (Table 1, Entries 1, 7).

To investigate the effect of solvents on the reaction, the reaction was carried out in various common solvents using Co NPs (8 mol%) as the catalyst. The progress of reactions was slow and the corresponding product was obtained in low yield when solvents such as toluene, acetonitrile, and ethanol were used (Table 1, Entries 8-10). The best result was obtained in

water by the use of 8 mol % of the catalyst (Table 1, Entry 5).

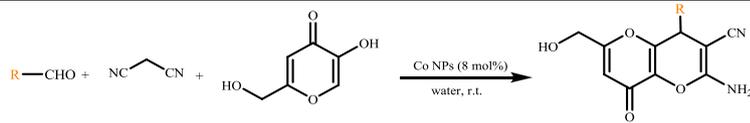
Having optimized reaction conditions in hand and in order to check the generality of the method, we expanded our results to various aldehydes, kept another component constant, and obtained corresponding pyranopyrane derivatives (**4a–4t**) in 80–98% yields. Interestingly, a variety of aldehydes including ortho-, meta-, and para-substituted benzaldehydes participated well in this reaction (Table 2, Entries 1-13). From the results shown in Table 2, it is evident that both electron-withdrawing and electron-donating groups substituted in aromatic aldehydes afforded fairly high yields of the desired cyclocondensation in the reaction with Kojic acid and malononitrile at ambient temperature in water.

To further expand the scope of the reaction, then, we turned our attention to examining the aliphatic and heteroaromatic substituted aldehydes

(thienyl, furyl, pyridyl) to the desired reaction (Table 2). According to the results, aliphatic aldehydes such as propionaldehyde, butyraldehyde, and pentanal react well in the procedure. The results in table 2 highlight a variety of structures accepted by this method to give fairly high yields of the desired

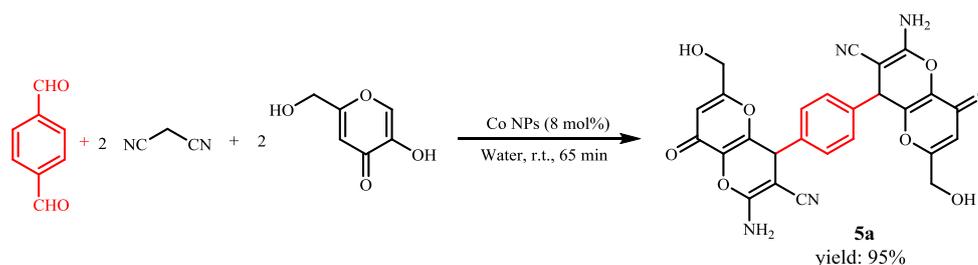
products. In order to further expand the scope of this methodology, a dialdehyde (terephthalaldehyde) was used and successfully converted to the corresponding bis-2-amino-dihydropyrano[3,2-b]pyran-3-carbonitrile in the presence of this catalyst (Scheme 2).

**Table 2.** Preparation of different products (**4a-4t**)



Entry	Product	R	Time (min)	Yield (%) <sup>a</sup>	Mp	
					Found	Reported
1	4a	C <sub>6</sub> H <sub>5</sub>	60	90	219-221	220-222 <sup>30</sup>
2	4b	2-ClC <sub>6</sub> H <sub>4</sub>	85	85	211-214	210-213 <sup>30</sup>
3	4c	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	70	85	239-242	240-242 <sup>30</sup>
4	4d	2-FC <sub>6</sub> H <sub>4</sub>	90	80	207-210	207-208 <sup>30</sup>
5	4e	3-FC <sub>6</sub> H <sub>4</sub>	75	87	221-224	220-223 <sup>30</sup>
6	4f	4-FC <sub>6</sub> H <sub>4</sub>	85	93	248-251	248-250 <sup>30</sup>
7	4g	3-BrC <sub>6</sub> H <sub>4</sub>	80	98	240-243	242-244 <sup>30</sup>
8	4h	3-MeC <sub>6</sub> H <sub>4</sub>	95	88	220-223	219-221 <sup>30</sup>
9	4i	3,5-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	60	93	272-275	271-273 <sup>30</sup>
10	4j	2-Thienyl	100	90	233-236	235-237 <sup>30</sup>
11	4k	2-Furyl	100	95	224-226	223-225 <sup>30</sup>
12	4l	4-Pyridyl	80	95	231-234	233-235 <sup>30</sup>
13	4m	3-Pyridyl	60	95	252-255	251-253 <sup>30</sup>
14	4n	2,3-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	60	95	253-256	—
15	4o	3,4-(OH) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	70	90	218-221	—
16	4p	Styryl	85	90	122-125	—
17	4q	5-Me-Furyl	70	93	243-245	—
18	4r	C <sub>2</sub> H <sub>5</sub>	90	70	156-158	—
19	4s	C <sub>3</sub> H <sub>8</sub>	90	78	185-187	184-186 <sup>24</sup>
20	4t	C <sub>4</sub> H <sub>9</sub>	90	83	167-169	—

<sup>a</sup>Isolated yields

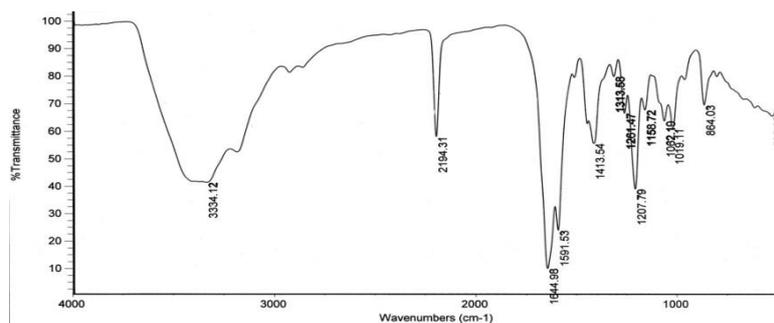


**Scheme 2.** Synthesis of compound **5a** catalyzed by Co NPs

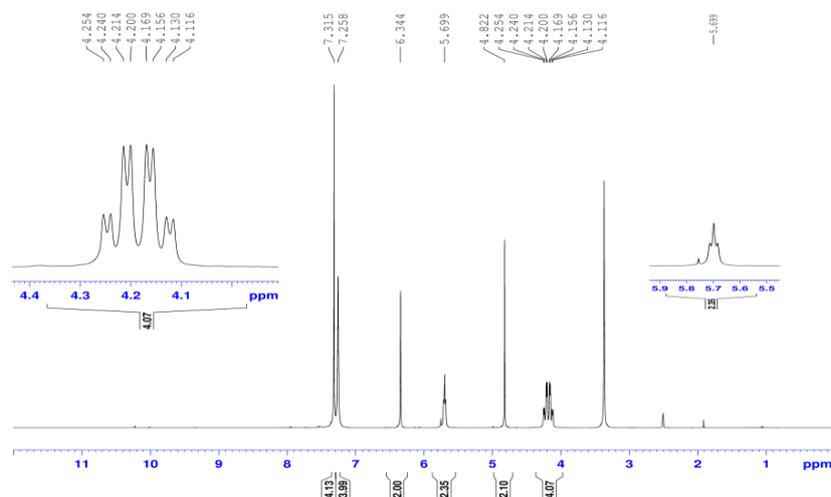
Kataev and his co-workers have reported  $\beta$ -cyclodextrin catalyzed synthesis of some 2-amino-dihydropyrano[3,2-b]pyran-3-carbonitriles [23]. In this protocol, high catalyst loading for the reaction and heat were used to increase the catalytic activity, but our protocol provides good catalytic activity without using any heating energy. Recently, Sadeghi and et al, reported synthesis of 2-amino-dihydropyrano[3,2-b] pyran-3-carbonitriles using sulfuric acid supported on silica nanoparticles [24]. The methodology shows random formation of nanoparticles and does not get the specific shape and size of nano-catalyst. It also suffers from limited substrate scope like aliphatic aldehydes. In our previous research, 2-amino-dihydropyrano [3,2-b] pyran-3-carbonitriles were synthesized under ultrasonic irradiations. Although the method used ultrasound irradiations in room temperature in water as a green method, but it suffers from limited substrate and useful procedure for aliphatic aldehydes. Our protocol uses a variety of different (hetero) aromatic aldehydes and overcomes the drawbacks [30]. Moreover, the catalyst separation process is very simple when using a magnet without the need for hazardous organic solvents.

### Structure investigation of new product **5a**

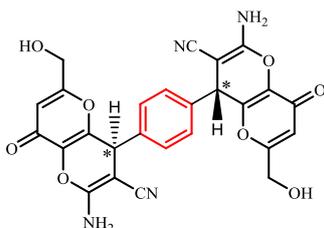
The structure of isolated product **5a** was confirmed by spectroscopic data such as: IR,  $^1\text{H-NMR}$  spectroscopy. In IR spectra, in region between  $\nu=3330\text{--}3350\text{ cm}^{-1}$ , symmetrical and unsymmetrical stretching frequency of  $\text{NH}_2$  is formed. The predominant absorbance peak in the region between  $\nu=2190\text{--}2200\text{ cm}^{-1}$  was due to the stretching frequency of nitrile group (Figure 1). The  $^1\text{H-NMR}$  spectra in  $\text{DMSO-d}_6$  exhibited the two singlet signals around  $\delta=7.20\text{--}7.30$  and  $\delta=9.31\text{--}9.32$  ppm corresponding to  $\text{NH}_2$  group and four equivalent hydrogens on the benzene ring (corresponding to aldehyde) in product **5a** confirming the formation of the desired products in reaction (Figure 2). The  $^1\text{H-NMR}$  spectra showed the two coupled signals around  $\delta=4.10\text{--}4.30$  and  $\delta=5.50\text{--}5.70$  ppm corresponding to  $\text{CH}_2$  and  $\text{OH}$  groups of corresponding compound. The methylene group on the hydroxymethyl substituent shows a complex splitting pattern than a simple doublet. This behavior is due to the existence of an asymmetric benzylic carbon in product **5a** that makes the two hydrogens become non-equivalence on methylene group (Figure 3). As shown, the diastereotopic hydrogens of  $\text{CH}_2$  group were coupled with hydrogen of hydroxyl with coupling constant of  $^3J_{\text{vic}} = 5.6\text{ Hz}$  (Figure 2).



**Figure 1.** FTIR spectra of compound **5a**



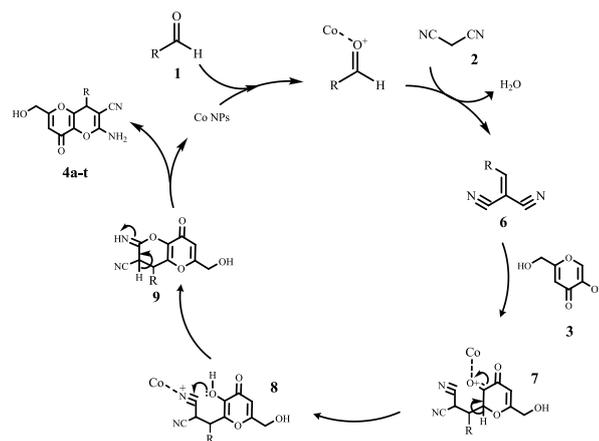
**Figure 2.**  $^1\text{H-NMR}$  spectra of compound **5a**



**Figure 3.** Structure of asymmetric benzylic carbons of product **5a**

Based on experimental study, a possible mechanism for the synthesis of the desired compound is outlined in Scheme 3. The Knoevenagel condensation between activated aldehyde **1** and malononitrile **2** in the presence of the catalyst generates the intermediate **6**. Subsequently, the

Michael addition of the kojic acid **3** to **6** in the presence of the catalyst gives **7**. Finally, cyclization of **7** to **8** which further cyclizes to give the desired product **4(a-t)** releases the catalyst for the next catalytic cycle.



Scheme 3. Possible mechanism

### The investigation of catalyst recovery

The recovery of the catalyst is a great advantage in reducing the overall cost in process chemistry and decreasing environmental pollution. It eliminates involvement in the synthesis and resale process. In the final phase of the study, the reusability of the catalyst, Co NPs, was evaluated in the model reaction. In this regard, the catalyst was recovered by a simple work-up using the magnetic decantation method and reused over four cycles without any apparent loss of activity for the same reaction. It is noteworthy that the yield of the product in the second, third, and fourth use was almost the same as in the first run (with the yields of the products **4a** being

90%, 90%, 89%, 88%, respectively). Also, the possibility of surface oxidation of nano-catalyst was studied. Therefore, the reusable catalysts were tested for the presence of oxygen by EDAX examination. Figure 4, shows EDAX patterns of the fresh and 4th recycle Co NPs. Based on the results, the total composition of cobalt was found in the resultant sample. However, EDAX result shows that the catalyst consists mainly of cobalt (97%), and the small amount of oxygen which is also present while no other elements were found using EDAX. This detected oxygen by EDAX might come from surface oxidation Co NPs during the reaction and/or after treatment.

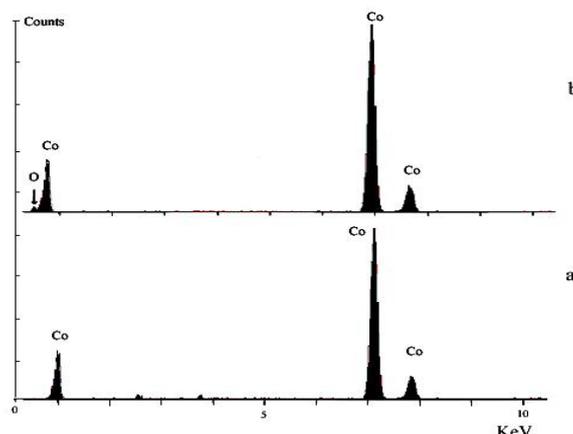
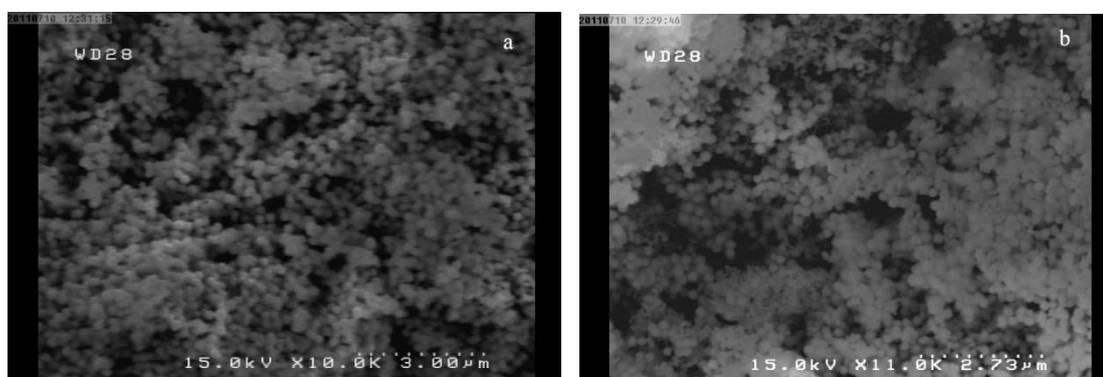


Figure 4. EDAX patterns of fresh (a) and 4th recycle (b) Co NPs

Then, the morphology investigation of fresh and recycled Co NPs was studied using SEM (Figure 5). The Figure 5a displays SEM analysis of fresh cobalt nanoparticles whereas Figure 5b displays SEM analysis of magnetically recycled cobalt nano-

catalyst after the fourth run. The detail analysis of recycled catalyst reveals that nanoparticles are spherical in shape along with somewhat more aggregation of particles (Figure 5b) than that of fresh nanoparticles (Figure 5a).

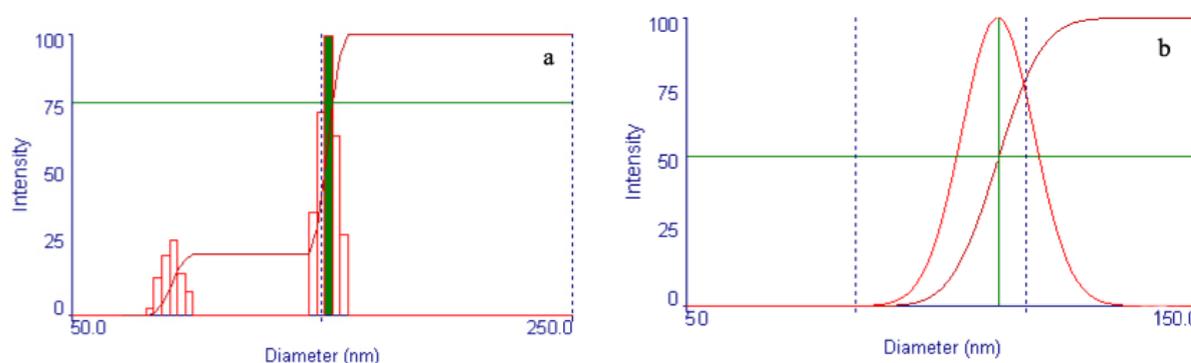


**Figure 5.** a) SEM image of fresh Co NPs, b) SEM image of Co NPs after fourth run

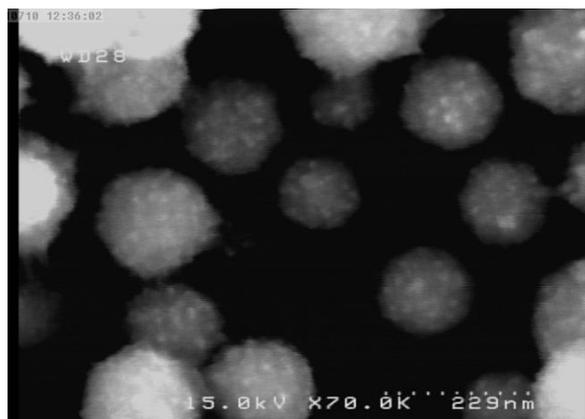
### **Characterization of synthesized cobalt nanoparticles**

The synthesized cobalt nanoparticles were characterized by SEM, and DLS analysis (Figure 6, 7). The particle size and size distribution of cobalt nanoparticle, as a critical property, have been determined by scanning electron microscopy (SEM), and dynamic light scattering (DLS) analysis. The particle

size was found to be in the range of 80-100 nm (Figure 6a, b). The SEM images also reveal that particles are spherical in shape and loosely agglomerated (Figure 7). Comparing the DLS and SEM results shows that the particles are in the size range 80-100 nm. In comparison, there is a good correlation between the DLS and SEM measurements.



**Figure 6.** Particle size distribution of the nanoparticles obtained by dynamic light scattering (DLS)



**Figure 7.** SEM image of synthesized cobalt nanoparticles

### Conclusion

In summary, we have shown the catalytic applicability of synthesized cobalt nanoparticles for coupling reaction of Kojic acid, malononitrile and different substituted aldehydes in aqueous media at ambient temperature. Under the optimized reaction conditions various aldehydes provided good to excellent yield of the respective products. Notably, the reaction does not require any heating energy and it was progressed with low catalyst loading and also executed under green conditions with good to excellent yields of the desired products with catalyst recyclability up to fourth runs. These conditions make the protocol an attractive one. This is one of the simple and ecological protocols for the synthesis of fused 6-membered heterocycles ring containing two oxygen atoms.

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