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Article

Ni(II), Co(II), and Cu(II) complexes incorporating 2-pyrazinecarboxylic acid: Synthesis, characterization, electrochemical evaluation, and catalytic activity for the synthesis of 2H-indazolo[2,1-*b*]phthalazine-triones

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ABSTRACT

Three complexes containing 2-pyrazinecarboxylate (pzca[−]), including [Ni(pzca)₂(H₂O)₂], [Co(pzca)₂(H₂O)₂], and [Cu(pzca)₂(H₂O)₂], have been synthesized and characterized using physico-chemical and spectroscopic methods. Furthermore, the structure of each complex was determined by single-crystal X-ray diffraction. All three complexes have an octahedral geometry, where the metal ion chelated by two carboxylate oxygens, two nitrogen atoms belonging to pyrazinic acid molecules, and two oxygen atoms of two water molecules. The catalytic activities of these complexes were also investigated in the green synthesis of 2H-indazolo[2,1-*b*]phthalazine-triones by the reaction of hydrazine hydrate with an arylaldehyde, phthalic anhydride, and dimedone in acetic acid.

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1. Introduction

Multi-component reactions (MCRs) have emerged as a powerful tool for the synthesis of novel and complex molecular structures because they exhibit several distinct advantages over conventional multi-step reactions including lower costs, shorter reaction times, and higher atom-economy [1]. Furthermore, MCRs are generally much more environmentally friendly and provide rapid access to large compound libraries with diverse functionalities [2,3].

There has always been considerable interest in the development of new methods for the synthesis of heterocyclic com-

pounds because of their wide range of potentially interesting biological properties and applications [4]. Amongst the large variety of heterocyclic compounds, those containing a phthalazine moiety have attracted increasing attention mainly because this unit is an important structural motif found in numerous biologically active organic compounds [5]. For example, phthalazine derivatives have been reported to possess anti-convulsant [6], cardiotonic [7], and vasorelaxant [8] activities, and significant research efforts have been directed towards the development of new methods for the synthesis of these compounds and their derivatives.

Although a variety of different catalysts have been used for

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the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones, the scope of these methods can be limited by the requirement for harsh and strongly acidic conditions [9], expensive catalysts [10], toxic organic solvents [11,12], long reaction times [13] and their tendency to produce low yields of the desired products [14]. Some of these issues can be overcome by using a metal complex as a catalyst. Transition metal complexes have attracted increasing levels of attention from a variety of different fields because of the ease with which they can be prepared, as well as their biological activity [15,16], variety of structure [17], and potential catalytic activities [18]. Although the catalytic activities of several different transition metal complexes towards MCRs have been reported extensively elsewhere in the literature [19], there have been no studies pertaining to the use of these catalysts for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones.

With this in mind, we have prepared a series of Ni(II), Co(II), and Cu(II) complexes incorporating 2-pyrazine carboxylic acid, and the resulting three complexes were fully characterized using a variety of different physicochemical and spectroscopic methods. These complexes have also been evaluated as catalysts in an environmentally friendly and efficient protocol for the four-component synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones (Scheme 1).

2. Experimental

2.1. Materials and instrumentation

2-Pyrazinecarboxylic acid, $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$, $\text{Co}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$, and $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$, as well as all of the solvents used in the current study were purchased from Merck (Darmstadt, Germany) and used without further purification. All of the other chemicals used in this study were either prepared in our laboratory or purchased from Sigma Aldrich or Fluka. Microanalyses for C, H, and N were determined on a ThermoFinnigan Flash Elemental Analyzer 1112EA (Bremen, Germany). The melting points (M.P.) of the products were measured on an Electrothermal-9100 apparatus (Electrothermal Engineering Ltd., Essex, UK) and have been reported as the uncorrected values. All of the reactions were monitored by thin layer chromatography (TLC) using a 3:1 (v/v) mixture of petroleum ether and ethyl acetate as the developing solvent. Fourier transform infrared (FT-IR) spectra were recorded on a Tensor 27 FT-IR spectrophotometer (Bruker Optics Inc. Billerica, MA, USA). ^1H and ^{13}C NMR spectra were recorded on a Bruker 300-MHz spectrometer using CDCl_3 as a solvent with TMS as an internal reference standard. Conductance measurements were recorded on a Metrohm 712 conductometer (Herisau, Switzerland) using DMSO as the solvent.

2.2. General procedure for the synthesis of the complexes

$[\text{Co}(\text{pzca})_2(\text{H}_2\text{O})_2]$, $[\text{Ni}(\text{pzca})_2(\text{H}_2\text{O})_2]$, and $[\text{Cu}(\text{pzca})_2(\text{H}_2\text{O})_2]$ were synthesized separately according to the procedure described below. A solution of metal nitrate salt (1 mmol) in 3 mL of ethanol (96%) was placed in the main arm of a branched tube, followed by 2-pyrazinecarboxylic acid (0.025 g, 2 mmol). Ethanol was then carefully added to fill the arms, and the tube was sealed. The ligand-containing arm was subsequently immersed in an oil bath and heated at 60 °C, while the other arm was kept at ambient temperature. Single crystals formed in the branched arm after 1 d under these conditions, which were collected by filtration and dried in a desiccator at ambient temperature over silica gel.

$[\text{Ni}(\text{pzca})_2(\text{H}_2\text{O})_2]$ (**1**). Yield: 0.237 g, 69%. M.P. 248 °C (decomp.). Molar conductivity (1 mmol/L, DMSO): 6.2 $\Omega^{-1} \text{cm}^2 \text{mol}^{-1}$. Anal. Calcd for $\text{C}_{10}\text{H}_{10}\text{N}_4\text{NiO}_6$ (340.90 g/mol): C, 35.2; H, 2.9; N, 16.4; found: C, 35.5; H, 2.8; N, 16.1%. FT-IR (KBr) cm^{-1} : $\nu(\text{OH})$ 3247, $\nu(\text{NH})$ 3074, $\nu_{\text{asy}}(\text{COO}^-)$ 1624, $\nu_{\text{sy}}(\text{COO}^-)$ 1357, $\nu(\text{C}=\text{N})$ 1585, $\nu(\text{C}=\text{C})$ 1470, $\nu(\text{C}-\text{O})$ 1288, $\nu(\text{Ni}-\text{O})$ 636, $\nu(\text{Ni}-\text{N})$ 467.

$[\text{Co}(\text{pzca})_2(\text{H}_2\text{O})_2]$ (**2**). Yield: 0.289 g, 85%. M.P. > 300 °C. Molar conductivity (1 mmol/L, DMSO): 8.4 $\Omega^{-1} \text{cm}^2 \text{mol}^{-1}$. Anal. Calcd for $\text{C}_{10}\text{H}_{10}\text{CoN}_4\text{O}_6$ (341.14 g/mol): C, 35.2; H, 2.9; N, 16.4; found: C, 35.0; H, 2.8; N, 16.3%. FT-IR (KBr) cm^{-1} : $\nu(\text{OH})$ 3251, $\nu(\text{NH})$ 3070, $\nu_{\text{asy}}(\text{COO}^-)$ 1639, $\nu_{\text{sy}}(\text{COO}^-)$ 1357, $\nu(\text{C}=\text{N})$ 1584, $\nu(\text{C}=\text{C})$ 1470, $\nu(\text{C}-\text{O})$ 1289, $\nu(\text{Co}-\text{O})$ 636, $\nu(\text{Co}-\text{N})$ 466.

$[\text{Cu}(\text{pzca})_2(\text{H}_2\text{O})_2]$ (**3**). Yield: 0.253 g, 73%. M.P. > 300 °C. Molar conductivity (1 mmol/L, DMSO): 4.7 $\Omega^{-1} \text{cm}^2 \text{mol}^{-1}$. Anal. Calcd for $\text{C}_{10}\text{H}_{10}\text{CuN}_4\text{O}_6$ (345.76 g/mol): C, 34.7; H, 2.9; N, 16.2; found: C, 34.5; H, 2.8; N, 16.4%. FT-IR (KBr) cm^{-1} : $\nu(\text{OH})$ 3250, $\nu(\text{NH})$ 3068, $\nu_{\text{asy}}(\text{COO}^-)$ 1621, $\nu_{\text{sy}}(\text{COO}^-)$ 1358, $\nu(\text{C}=\text{N})$ 1585, $\nu(\text{C}=\text{C})$ 1470, $\nu(\text{C}-\text{O})$ 1286, $\nu(\text{Cu}-\text{O})$ 625, $\nu(\text{Cu}-\text{N})$ 452.

2.3. Crystal structure determination

Crystals of complexes **1–3** suitable for analysis were mounted on Mitegen™ loops and placed in the cold nitrogen stream of the Bruker D8 Venture Photon 100 CMOS diffractometer. Hemispheres of data were collected using the APEX2 software [20] and the raw data reduced to F_o^2 values using the SAINT software [20], which was also used to achieve the global refinement of the unit cell parameters. Corrections for the absorption and merging of equivalent reflections were carried out using SADABS [20] and the structures were solved using a combination of Patterson and direct methods (SHELXT [20]). Full-matrix least-squares refinement of the structures was achieved using SHELXL-2013 [21]. All of the hydrogen atoms attached to carbon were placed in their calculated positions and those attached to oxygen were placed in positions derived

Scheme 1. Four-component synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones.

from difference maps after, and their coordinates were adjusted to give O–H = 0.84 Å. All of these atoms were included as riding contributions with isotropic displacement parameters tied to those of the attached atoms. The details of crystallographic analysis are shown in Table 1.

2.4. General procedure for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones

A mixture of hydrazinium hydrate (1.2 mmol), phthalic anhydride (1 mmol), dimedone (1 mmol), an aryl aldehyde (1 mmol) and [Co(pzca)₂(H₂O)₂] (20 mol%), [Ni(pzca)₂(H₂O)₂] (25 mol%) or [Cu(pzca)₂(H₂O)₂] (20 mol%) in 5 mL of acetic acid was heated at 50 °C to give the corresponding 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione derivative. Upon com-

pletion of the reaction, as determined by TLC, the solvent was evaporated to give a residue, which was mixed with 5 mL of EtOH. The catalyst was removed by centrifugation and the crude product was recrystallized from a mixture of ethanol and water.

The scope and efficiency of this reaction for the synthesis of a wide variety of substituted 2*H*-indazolo[2,1-*b*]phthalazine-triones were evaluated under the optimized conditions using the title metal complexes. All of the products obtained from these reactions were identified through a comparison of their spectral data and melting points with those of the authentic samples. The compounds were also characterized by IR spectroscopy, as well as ¹H and ¹³C NMR analysis. The spectral data for selected compounds are as follows.

3,4-Dihydro-3,3-dimethyl-13-phenyl-2*H*-indazolo[2,1-*b*]

Table 1

Crystallographic data for complexes 1–3.

Complex	1	2	3
Chemical formula	C ₁₀ H ₁₀ N ₄ NiO ₆	C ₁₀ H ₁₀ CoN ₄ O ₆	C ₁₀ H ₁₀ CuN ₄ O ₆
Formula weight	340.93	341.15	345.76
Temperature (K)	100(2)	100(2)	100(2)
Wavelength (Å)	1.54178	1.54178	1.54178
Crystal size (mm)	0.100 × 0.120 × 0.140	0.134 × 0.151 × 0.239	0.065 × 0.070 × 0.130
Crystal habit	pale blue-green block	orange block	light blue-green block
Crystal system	monoclinic	monoclinic	monoclinic
Space group	<i>P</i> 1 2 ₁ /c 1	<i>P</i> 1 2 ₁ /c 1	<i>P</i> 1 2 ₁ /c 1
Unit cell dim.			
<i>a</i> (Å)	5.2207(2)	5.2182(1)	5.3944(2)
<i>b</i> (Å)	10.9895(4)	11.1162(3)	10.8893(4)
<i>c</i> (Å)	10.1603(4)	10.1619(3)	10.2217(4)
α (°)	90	90	90
β (°)	100.4270(12)	100.1960(7)	99.0050(16)
γ (°)	90	90	90
<i>V</i> (Å ³)	573.30(4)	580.15(3)	593.03(4)
<i>Z</i>	2	2	2
ρ (g/cm ³)	1.975	1.953	1.936
μ (mm ⁻¹)	2.854	12.004	2.999
<i>F</i> (000)	348	346	350
θ range for data coll. (°)	5.99 to 72.31	5.95 to 72.32	5.98 to 72.25
Index ranges	–6 ≤ <i>h</i> ≤ 6 –13 ≤ <i>k</i> ≤ 13 –11 ≤ <i>l</i> ≤ 12	–5 ≤ <i>h</i> ≤ 6 –13 ≤ <i>k</i> ≤ 12 –11 ≤ <i>l</i> ≤ 12	–6 ≤ <i>h</i> ≤ 6 –12 ≤ <i>k</i> ≤ 13 –12 ≤ <i>l</i> ≤ 12
Refls. coll.	4829	6050	5224
Ind. refls.	1097 [<i>R</i> _{int} = 0.0230]	1134 [<i>R</i> _{int} = 0.0233]	1157 [<i>R</i> _{int} = 0.0219]
Coverage (%)	96.8	98.7	98.6
Abs. corr.	multi-scan	multi-scan	multi-scan
Max. and min. trans.	0.763 and 0.691	0.296 and 0.162	0.829 and 0.697
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$	$\Sigma w(F_o^2 - F_c^2)^2$	$\Sigma w(F_o^2 - F_c^2)^2$
Data/restraints/params.	1097/0/98	1134/0/97	1157/0/97
GoF on <i>F</i> ²	1.135	1.128	1.132
Final <i>R</i> indices			
Data; <i>I</i> > 2σ(<i>I</i>)	1077; <i>R</i> ₁ = 0.0238, <i>wR</i> ₂ = 0.0668	1101; <i>R</i> ₁ = 0.0226, <i>wR</i> ₂ = 0.0621	1103; <i>R</i> ₁ = 0.0244, <i>wR</i> ₂ = 0.0695
All data	<i>R</i> ₁ = 0.0242, <i>wR</i> ₂ = 0.0673	<i>R</i> ₁ = 0.0233, <i>wR</i> ₂ = 0.0627	<i>R</i> ₁ = 0.0258, <i>wR</i> ₂ = 0.0709
Extinction coefficient	0.0078(9)		
Largest diff. peak and hole (e Å ⁻³)	0.319 and –0.403	0.202 and –0.384	0.298 and –0.402
R.M.S. dev. from mean (e Å ⁻³)	0.070	0.088	0.084
Wght. params. ^a	<i>a</i> = 0.373; <i>b</i> = 0.3440	<i>a</i> = 0.0376; <i>b</i> = 0.2695	<i>a</i> = 0.0408; <i>b</i> = 0.3857

^a Weighting scheme: $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$, where $P = (F_o^2 + 2F_c^2)/3$.

phthalazine-1,6,11(13*H*)-trione (**2a**). M.P. = 207–209 °C. FT-IR (KBr) ($\nu_{\max}$, cm^{-1}): 2957, 1663, 1575. ^1H NMR (300 MHz, CDCl_3 , 25 °C, ppm) δ = 1.21 (s, 6H), 2.35 (d, J = 6.03 Hz, 1H), 2.47 (d, J = 5.7 Hz, 1H), 3.24 (1H, dd, J = 19.03, 2.07 Hz), 3.41 (d, 1H, J = 19.03 Hz), 6.45 (s, 1H), 7.21–7.43 (m, 4H, arom), 7.84–7.86 (m, 2H, arom), 8.26–8.36 (m, 2H, arom). ^{13}C NMR (125 MHz, CDCl_3 , 25 °C, ppm) δ = 28.4, 29.62, 35.8, 39.19, 42.00, 51.88, 119.73, 127.50, 128.28, 128.86, 129.12, 129.19, 129.52, 129.87, 130.12, 130.22, 134.69, 135.67, 137.55, 145.24, 152.01, 155.42, 157.18, 192.5.

3,4-Dihydro-3,3-dimethyl-13-(4-methylphenyl)-2*H*-indazolo [2,1-*b*] phthalazine-1,6,11(13*H*)-trione (**2b**). M.P. = 225–227 °C. FT-IR (KBr) ($\nu_{\max}$, cm^{-1}): 2958, 1668, 1630. ^1H NMR (300 MHz, CDCl_3 , 25 °C, ppm) δ = 1.17 (s, 6H), 2.25 (s, 3H), 2.28 (s, 2H), 3.18 and 3.37 (AB system, s, 2H, J = 18.85 Hz), 6.36 (s, 1H), 7.08–7.2 (m, 4H), 7.8 (m, 2H), 8.2–8.3 (m, 2H). ^{13}C NMR (125 MHz, CDCl_3 , 25 °C, ppm) δ = 21.6, 28.8, 29.1, 35.0, 38.4, 51.3, 65.1, 118.9, 127.4, 128.0, 128.3, 129.3, 129.5, 129.7, 133.8, 134.8, 138.8, 151.1, 154.6, 156.3, 192.5.

3. Results and discussion

3.1. Characterization of the complexes

All three complexes were synthesized according to the reaction shown in Scheme 2, with pyrazine carboxylic acid being reacted with the appropriate metal salt in a 2:1 molar ratio. The resulting complexes were found to be stable in air and soluble in several organic solvents, including DMSO and DMF. However, the complexes were found to be insoluble in methanol, *n*-hexane, and diethyl ether. The molar conductivities of these complexes were found to be in agreement with their non-electrolytic nature.

The ORTEP representations of the asymmetric unit of complexes **1–3** are shown in Fig. 1. These drawings show that all three complexes have similar structural features, including a *trans*-[diaquabis(pyrazine-2-carboxylato)M(II)] (*M* = Ni, Co, Cu) moiety with crystallographically-imposed centrosymmetry. They have all been structurally characterized previously [22–24], and all of the metrical parameters observed in the current study are quite comparable to those in prior reports, although the *su*'s are slightly smaller due to the low temperature of the data collection (100 K).

For the FT-IR studies, the most prominent peaks detected in

Scheme 2. Schematic diagram for the complexation process.

the IR spectra of complexes **1–3** in the 400–4000 cm^{-1} region are listed in the Experimental section. These data show that individual molecules of 2-pyrazine carboxylic acid (in deprotonated form) were binding to the metal center through one of their ring nitrogen atoms and one of their carboxylate oxygen atoms. The IR spectra also contained stretching frequency bands where the asymmetric-symmetric separations [$\nu_{\text{asy}}(\text{COO}^-) - \nu_{\text{sy}}(\text{COO}^-)$] were greater than 200 cm^{-1} (i.e., 267, 282, and 263 cm^{-1} for compounds **1–3**, respectively), which indicated that the COO^- moiety of 2-pyrazine carboxylic acid unit was coordinated to the metal centers as a monodentate ligand [25]. The IR spectra of all three complexes contained a band at 1470 cm^{-1} , which was assigned to the $\nu(\text{C}=\text{C})$ stretching vibrations of the aromatic rings [26,27]. Broad peaks were also observed in the range of 3251–3247 cm^{-1} for all three complexes, which were attributed to the OH stretching vibrations of water molecules [28,29].

Cyclic voltammograms were recorded in a 1 mmol/L solutions of each complex in DMSO containing 0.1 mol/L tetrabutylammonium perchlorate (TBAP) as a supporting electrolyte by scanning the potential from –1 to 1 V. A three-electrode assembly was employed using an Ag/AgCl electrode as a reference electrode, a platinum wire as a counter electrode and a glassy carbon electrode as the working electrode. The voltammogram obtained for the Cu(II) complex is shown in Fig. 2.

As shown in Fig. 2, the cyclic voltammogram the Cu(II) complex was characterized by a pair of well defined oxidation and reduction peaks at –281 and –352 mV, which had peak currents of 85.6 and –25.9 μA , respectively. The peak-to-peak potential separation (ΔE_p) of this complex was found to be 71 mV, and the half-wave potential was 316.5 mV. Irreversible redox peaks were also observed at 691 and 254 mV. The ratios of the anodic to cathodic peak currents correspond to the chemical changes that occur during the electron transfer processes of $\text{Cu(II)} \rightarrow \text{Cu(I)} \rightarrow \text{Cu(0)}$.

Redox peaks were observed at 52 and –292 mV for the Co(II) complex, and –110 and –215 mV for the Ni(II) complex.

Fig. 1. ORTEP drawings of $[\text{Ni}(\text{pzca})_2(\text{H}_2\text{O})_2]$ (**1**), $[\text{Co}(\text{pzca})_2(\text{H}_2\text{O})_2]$ (**2**), and $[\text{Cu}(\text{pzca})_2(\text{H}_2\text{O})_2]$ (**3**).

Fig. 2. Cyclic voltammogram of $[\text{Cu}(\text{pzca})_2(\text{H}_2\text{O})_2]$.

The peaks observed in all three complexes with potentials more positive than 500 mV were attributed to the oxidation of the pyrazine ring of the ligand.

3.2. Catalytic activity

The reaction of benzaldehyde with hydrazine hydrate, dimedone, and phthalic anhydride was selected as a model reaction to optimize the conditions of the MCR for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones. The reaction was conducted in the presence of all three metal catalysts in a variety of different solvents, and the results are summarized in Table 2. Higher yields and shorter reaction times were obtained when the reaction was carried out in acetic acid.

In a separate screening study, the condensation of hydra-

Table 3

Optimization of the amounts of complexes **1–3** charged as catalysts to the four-component synthesis of 3,4-dihydro-3,3-dimethyl-13-phenyl-2*H*-indazolo[1,2-*b*]phthalazine-1,6,11(13*H*)-trione via the reaction of benzaldehyde with hydrazine hydrate, dimedone, and phthalic anhydride in acetic acid at 50 °C.

Amount of catalyst (mol%)			Time (min)			Isolated yield (%)		
1	2	3	1	2	3	1	2	3
—	—	—	60	60	60	21	21	21
0.07	0.05	0.05	60	40	60	73	80	72
0.15	0.10	0.10	50	30	55	78	85	80
0.20	0.15	0.15	40	23	40	87	90	88
0.25	0.20	0.20	20	15	30	93	94	92
0.27	0.25	0.25	20	15	30	93	94	92

zine hydrate with benzaldehyde, phthalic anhydride, and dimedone was conducted in acetic acid in the presence of different quantities of the catalysts (Table 3). Notably, the results of these experiments revealed that the model MCR gave a very low yield of the desired 3,4-dihydro-3,3-dimethyl-13-phenyl-2*H*-indazolo[1,2-*b*]phthalazine-1,6,11(13*H*)-trione product when it was conducted in the absence of the title metal complexes.

With the optimized conditions in hand, we proceeded to evaluate the scope of this method using a variety of different aromatic aldehydes in the presence of complexes **1–3**, which were used as catalysts. Notably, a variety of different aromatic aldehydes, including *ortho*-, *meta*-, and *para*-substituted aryl aldehydes, all reacted smoothly under the optimized reaction conditions to give the corresponding products in good to excel-

Table 2

Optimization of times and yields in various solvents for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones from the reaction of benzaldehyde with hydrazine hydrate, dimedone, and phthalic anhydride.

Solvent	Amount of catalyst (mol%)			Temperature (°C)	Time (min)			Isolated yield (%)		
	1	2	3		1	2	3	1	2	3
EtOH	0.2	0.1	0.1	reflux	90	60	60	50	60	55
THF	0.1	0.2	0.2	rt	120	80	120	trace	30	20
EtOH/ H ₂ O	0.25	0.1	0.2	50	60	120	60	30	70	40
CH ₂ Cl ₂	0.2	0.2	0.25	reflux	120	120	120	20	40	25
CH ₃ COOH	0.25	0.25	0.2	rt	80	60	60	68	70	72
CH ₃ COOH	0.2	0.2	0.2	30	40	40	45	90	88	90
CH ₃ COOH	0.25	0.2	0.2	50	20	15	30	93	94	92
CH ₃ COOH	0.25	0.2	0.2	60	20	15	30	92	94	91

Experimental conditions: benzaldehyde (1 mmol), hydrazine hydrate (1.2 mmol), dimedone (1 mmol), phthalic anhydride (1 mmol) and the catalyst in solvent (5 mL).

Table 4

Four-component synthesis of a series of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives by the reaction of phthalic anhydride with hydrazine monohydrate, dimedone, and a series of aromatic aldehydes in the presence of complexes **1–3** as the reaction catalyst.

Entry	Aldehyde	Time (min)			Isolated yield (%)			M.P. (°C)	
		1	2	3	1	2	3	Found	Reported
1	PhCHO	20	15	30	93	94	92	204–206	204–206 [30]
2	3-O ₂ NC ₆ H ₄ CHO	18	12	25	91	93	89	269–270	270–272 [30]
3	4-ClC ₆ H ₄ CHO	15	14	27	90	89	88	262–263	262–264 [30]
4	2,4-Cl ₂ C ₆ H ₃ CHO	13	10	25	89	90	90	219–221	219–221 [31]
5	4-MeC ₆ H ₄ CHO	30	20	35	88	88	87	228–229	227–229 [30]
6	4-O ₂ NC ₆ H ₄ CHO	16	10	22	86	92	90	223–226	222–225 [30]
7	4-OMeC ₆ H ₄ CHO	25	25	40	80	89	86	217–219	218–220 [32]

Table 5

Comparison of the Ni(II), Co(II), and Cu(II) complexes **1–3** with several other previously reported catalysts for the synthesis of 3,4-dihydro-3,3-dimethyl-13-phenyl-2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione.

Catalyst	Reaction conditions	Time (min)	Yield (%)	Ref.
SBA-15 (0.02 g)	TFE, 65 °C	180	92	[33]
Ce(SO ₄) ₂ ·4H ₂ O (10 mol%)	Solvent free, 125 °C	6	78	[14]
PEG-OSO ₃ H (8 mol%)	Solvent free, 80 °C	13	87	[34]
[Bmim]Br (0.5 g)	Stirring, rt	180	31	[35]
[Hnhp][HSO ₄] (5 mol%)	Solvent free, 80 °C	7	88	[36]
CAN/PEG400 (5 mol%)	50 °C	120	94	[13]
<i>p</i> -Toluenesulfonic acid (30)	80 °C	10	86	[30]
1 (0.25 mol%) ^a	CH ₃ COOH, 50 °C	20	93	
2 (0.20 mol%) ^a	CH ₃ COOH, 50 °C	15	94	
3 (0.20 mol%) ^a	CH ₃ COOH, 50 °C	30	92	

^a This work.

lent yields. As shown in Table 4, the aldehydes bearing both electron-donating and electron-withdrawing groups participated in the condensation reaction with equal efficiency. Thus, the nature and position of the substituents on the aromatic ring had no discernible impact on the success of the reaction.

Finally, to demonstrate the efficiency of our newly developed method, the performance of catalysts **1–3** was compared with those of several other catalysts that had been reported previously for the synthesis of 3,4-dihydro-3,3-dimethyl-13-phenyl-2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione derivatives. As shown in Table 5, our newly developed method offers several significant advantages of the other existing methods, such as a cleaner reaction profile, easier handling of the catalyst, shorter reaction times, and environmental com-

Scheme 3. Proposed mechanism for the synthesis of the 2*H*-indazolo[2,1-*b*]phthalazine-triones catalyzed by [M(pzca)₂(H₂O)₂] (M = Ni(II), Co(II), Cu(II)).

Fig. 3. Reusability of the complexes **1–3** as catalysts for the reaction of hydrazine monohydrate with phthalic anhydride, benzaldehyde, and dimedone.

patibility. Overall, the use of the complexes prepared in the current study allowed for the preparation of the desired products in satisfactory yields using lower temperatures over shorter reaction times, and without the need for expensive catalysts.

A mechanism was proposed for the current reaction using the metal catalysts and is shown in Scheme 3. An initial Knoevenagel condensation reaction between the aryl aldehyde and dimedone in the presence of a catalytic amount of the metal complex would afford intermediate (A). The condensation of hydrazine monohydrate with phthalic anhydride would afford phthalhydrazide (B) with the loss of water. The subsequent 1,4-conjugate addition of phthalhydrazide (B) to intermediate (A), followed by the sequential cyclization and tautomerization of the addition product would give the corresponding product (C). Kiasat et al. [37] previously performed density functional theory calculations on the nature of each step of this mechanism, which confirmed the accuracy of the proposed mechanism.

The recyclability properties of the three different catalysts were also investigated using the model reaction between hydrazine monohydrate, phthalicanhydride, benzaldehyde and dimedone for the preparation of 3,4-dihydro-3,3-dimethyl-13-phenyl-2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione (Table 4, entry 1). Upon completion of the reaction, the solvent was evaporated to give a residue, which was suspended in 5 mL EtOH. The catalyst was then removed by centrifugation and the crude product was recrystallized from a mixture of ethanol and water. The pure products were characterized by a comparison of their physical data with those of the known compounds. The recovered catalysts could be reused at least three times without any discernible loss in their activities (Fig. 3).

4. Conclusions

Three complexes of Ni(II), Co(II), and Cu(II) containing pyrazine carboxylic acid have been synthesized and structurally characterized. All these complexes were found to be octahedral in geometry, and their metal ions were surrounded by the nitrogen and oxygen atoms of 2-pyrazinecarboxylate (pzca[−]), as

well as the oxygen atom of coordinated water molecules. These complexes performed as efficient catalysts for the one-pot, four-component synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives. The key advantages of this synthetic methodology include its high efficiency, generality, good to excellent yields of the desired products, short reaction time, simplicity, low reaction temperature, ease of product isolation, clean reaction profile, avoidance of hazardous catalysts and solvents, and general agreement with the principles of green chemistry, making it a useful and attractive process for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones.

Supplementary data

CCDC 1040555-1040557 contain the supplementary crystallographic data for complexes **1–3**. These data can be obtained free of charge via <http://www.ccdc.cam.ac.uk/conts/retrieving.html>, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk

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Graphical Abstract

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Ni(II), Co(II), and Cu(II) complexes incorporating 2-pyrazinecarboxylic acid: Synthesis, characterization, electrochemical evaluation, and catalytic activity for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones

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Three complexes containing pyrazine carboxylic acid, with the formulas $[\text{Ni}(\text{pzca})_2(\text{H}_2\text{O})_2]$, $[\text{Co}(\text{pzca})_2(\text{H}_2\text{O})_2]$, and $[\text{Cu}(\text{pzca})_2(\text{H}_2\text{O})_2]$, have been synthesized and fully characterized. These complexes were also evaluated as catalysts for the efficient one-pot four-component synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones.

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