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A concise synthesis of furo[3,2-c]coumarins catalyzed by nanocrystalline $ZnZr_4(PO_4)_6$ ceramics under microwave irradiation

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Abstract: A simple and concise method catalyzed by nanocrystalline $ZnZr_4(PO_4)_6$ ceramics has been reported for the synthesis of a series of *trans*-2-benzoyl-3-(aryl)-2*H*-furo[3,2-c]chromen-4(3H)-ones using a multicomponent reaction of 2,4′-dibromoacetophenone, benzaldehydes and 4-hydroxycoumarin under microwave irradiation. This method provides several advantages including easy work-up, excellent yields, short reaction times, using of microwave as clean method, recoverability of the catalyst and little catalyst loading.

Keywords: Microwave irradiation, $ZnZr_4(PO_4)_6$ ceramics, furo[3,2-c]coumarins, nanocatalyst, One-pot

1. Introduction

Furocoumarins belong to an important class of compounds which show a wide range of biological activities such as antifungal [1], antibacterial [2], vasorelaxant [3], and can also serve as nuclear factor kappa B (NF-κB) inhibitors [4-5] and HIV-1 integrase inhibitors [6]. The synthesis of bioactive heterocycles from readily available starting materials using one-pot multicomponent reactions (MCRs) has gained significant interest both from synthetic and medicinal chemists. Multi-component reactions present a wide range of possibilities for synthesis of bioactive compounds [7-8]. Therefore, searching for efficient and concise techniques for the synthesis of furocoumarins through multicomponent reactions is a remarkable challenge. A number of methods has been developed for the synthesis of furocoumarins in the presence of diverse catalysts such as pyridine or a mixture of AcOH and $AcONH_4$ [9], ionic liquid [BMIm]OH [10], $Pd(CF_3COO)_2$ [11], $CuBr_2$ [12], N-methylimidazolium [13], Et_3N [14], Bu_3P and Et_3N [15], polyphosphoric acid or KOH [16] and $Rh_2(OAc)_4$ [17]. However, some of the reported methods tolerate disadvantages including long reaction times, harsh reaction conditions and use of toxic and non-reusable catalyst. Therefore, to avoid these limitations, the exploration of an efficient, easily available catalyst with high catalytic activity and short reaction time for the preparation of Furocoumarins is still favored. The possibility of accomplishing multicomponent reactions under microwave irradiation with a heterogeneous catalyst could improve their effectiveness from operating cost and ecological points of view [18-19]. Microwave irradiation (MWI) is used for a variety of organic syntheses due to short reaction times, easy workup and excellent yields. The scrutinized rate acceleration upon microwave irradiation is due to material–wave interactions leading to thermal and particular effects. The reaction mixture is heated from the inside since the microwave energy is transfered directly to the reagents [20-22]. The solid catalysts absorb microwave irradiation, thus they can serve as an internal heat source for the reactions.

Recently, nanocatalysts have emerged as an alternating method for the improvement of many important organic reactions. However, when the size of active site is reduced to nanoscale dimensions, the surface free energy is increased significantly [23].

According to the above results we used nano $ZnZr_4(PO_4)_6$ for the synthesis of furocoumarins. In this study, we report the successful synthesis of nano-$ZnZr_4(PO_4)_6$ as an efficient and green catalyst.

$ZnZr_4(PO_4)_6$ structure ceramics have been interested because of their unique properties and potential applications in diverse fields [24-25].

Herein, we wish to report the use of nano-$ZnZr_4(PO_4)_6$ as an efficient catalyst for the preparation of *trans*-2-benzoyl-3-(aryl)-2H-furo[3,2-c]chromen-4(3*H*)-ones using a multicomponent reaction of 2,4′-dibromoacetophenones, benzaldehydes and 4-hydroxycoumarins under microwave irradiation (Scheme 1).

Scheme 1.

2 Experimental

2.1. Chemicals and apparatus

All organic materials were purchased commercially from Sigma–Aldrich and Merck and were used without further purification. A multiwave ultrasonic generator (Sonicator 3200; Bandelin, MS 73, Germany), equipped with a converter/transducer and titanium oscillator (horn), 12.5 mm in diameter, operating at 20 kHz with a maximum power output of 200 W, was used for the ultrasonic irradiation. The ultrasonic generator automatically adjusted the power level. All melting points are uncorrected and were determined in capillary tube on Boetius melting point microscope. FT-IR spectra were recorded with KBr pellets using a Magna-IR, spectrometer 550 Nicolet. NMR spectra were recorded on a Bruker 400 MHz spectrometer with DMSO-d_6 as solvent and TMS as internal standard. CHN compositions were measured by Carlo ERBA Model EA 1108 analyzer. Powder X-ray diffraction (XRD) was carried out on a Philips diffractometer of X'pert Company with monochromatized Zr Kα radiation (λ= 1.5406 Å). In order to investigate the particle size and morphology of the synthesis structures nano-$ZnZr_4(PO_4)_6$, FE-SEM images of the products visualized by a HITACHI S4160 Field Emission Scanning Electron Microscope.

2.2. Preparation of nanocrystalline $ZnZr_4(PO_4)_6$ ceramics

$ZrOCl_2$ was used as zirconium source. Firstly 1 mmol of $ZrOCl_2.8H_2O$ and 1 mmol of $Zn(NO_3)_2{\cdot}6H_2O$ were added in 15 mL of $HO(CH_2)_2OH$ and sonicated at 30 W power to completely dissolution. Afterward 0.8 mL H_3PO_4 (85%), 4 mmol of NH_4Cl and 1.4 mL of CH_3NH_2 water solution (25.0-30.0%) were added consecutively and sonicated for 30 min. Then, the reaction mixture was transferred into a Teflon-lined autoclave under autogenous pressure at 200 ^oC for 5 days. When the reaction was completed, dispersed precipitate was obtained. The solid was filtered and washed with distilled water and ethanol several times. Subsequently product was dried

at 50 ^{o}C for 5 h and calcined at 700 ^{o}C for 2 h. Afterward the solid was added in 20 mL of DMF and sonicated at 95 W power for 2 h. Finally the resulting product was filtered, washed with distilled water and absolute ethanol and dried at 150 ^{o}C for 2 h in vacuum to afford pure nano-$ZnZr_4(PO_4)_6$ ceramics.

2.3.General procedure for the synthesis of furo[3,2-c]coumarins

A mixture of pyridine (1 mmol) and 2,4′-dibromoacetophenone (1 mmol) was stirred for 1 min to which, subsequently, aromatic aldehydes (1 mmol), 4-hydroxycoumarin (1 mmol) and nano $ZnZr_4(PO_4)_6$ (2 mol%) in 12 mL ethanol was added under microwave irradiation (400 W) for the specific time. After completion of the reaction (TLC), hot CH_3OH was added. The catalyst was insoluble in hot CH_3OH and it could therefore be recycled by a simple filtration. The solvent was evaporated and the solid obtained recrystallized from ethanol to afford the pure furo[3,2-c]coumarins.

2.4. Spectral Data

trans-2-4'-bromo-benzoyl-3-phenyl-2H-furo[3,2-c]chromen-4(3H)-one (4a):

White powder, m.p 243-244 ºC, IR (KBr) cm^{-1}: 2931, 2853, 1718, 1644, 1452, 1404, 1025, 753, 576; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.82 (CH, 1H, d, *J*= 5.2 Hz), 6.11 (CH, 1H, d, *J*= 5.2 Hz), 6.88-7.03 (m, 7H), 7.34 (m, 1H), 7.55 (m, 2H), 7.84 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 48.32, 92.19, 105.22, 112.22, 117.32, 121.25, 122.38, 123.98, 127.24, 128.62, 129.22, 130.50, 131.96, 133.20, 134.42, 138.88, 155.62, 159.41, 166.34, 192.03; Anal. Calcd for $C_{24}H_{15}BrO_4$:C, 64.45; H, 3.38; Found: C, 64.33; H, 3.27.

trans-2-4'-bromo-benzoyl-3-(3-methylphenyl)-2H-furo[3,2-c]chromen-4(3H)-one (4b)

White powder, m.p 222-224ºC, IR (KBr) cm^{-1}: 2927, 2854, 1720, 1648, 1455, 1405, 1026, 753, 576; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.50 (CH_3, 3H), 4.80 (CH, 1H, d, *J*= 4.4 Hz), 6.09 (CH, 1H, d, *J*= 4.4 Hz), 7.04 (m, 6H), 7.34 (m, 1H), 7.60 (m, 2H), 7.99 (m, 3H);^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.2, 48.78, 92.11, 104.54, 112.02, 117.22, 120.93, 122.31, 124.25, 127.23, 127.99, 128.32, 128.45, 129.11, 130.51, 132.46, 133.25, 134.40, 139.12, 155.61, 159.42, 166.36, 192.02; Anal. calcd for$C_{25}H_{17}BrO_4$: C, 65.09; H, 3.71; Found: C, 65.16; H, 3.88;

trans-2-4'-bromo-benzoyl-3-(2-methylphenyl)-2H-furo[3,2-c]chromen-4(3H)-one (4c)

White powder,m.p 171-173 ºC, IR (KBr) cm^{-1}:2923, 2851, 1721, 1645, 1453, 1407, 1029, 575; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.43 (CH_3, 3H), 5.20 (CH, 1H, d, *J* = 5.6 Hz), 6.02 (CH, 1H, d, *J* = 5.6 Hz), 6.89 (m, 1H), 7.27 (m, 7H), 7.60 (d, *J*= 8.8 Hz, 2H), 7.83 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.3, 48.79, 92.14, 104.63, 112.05,117.25, 120.95, 122.33, 124.26, 127.25, 128.08, 128.48, 129.14, 130.57, 130.59, 132.46, 133.27, 134.44, 139.15, 155.64, 159.44, 166.37, 192.10; Anal. calcd for$C_{25}H_{17}BrO_4$: C, 65.09; H, 3.71; Found: C,65.12; H, 3.82;

trans-2-4'-bromo-benzoyl-3-(4-chlorophenyl)-2H-furo[3,2-c]chromen-4(3H)-one (4d)

White powder, m.p 250-252 ºC, IR (KBr) cm^{-1}: 2924, 2824, 1722, 1646, 1412, 1024, 752, 534; ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 4.77 (CH, 1H, *J*= 5.0 Hz), 6.63 (CH, 1H, *J*= 5.0 Hz), 7.22-7.26 (m, 2H), 7.29-7.32 (m, 2H), 7.32 (m, 3H), 7.50-8.03 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 49.66, 93.51, 105.22, 112.20, 117.35, 121.28, 122.45, 124.32, 127.25, 128.63, 129.19, 130.59, 133.04, 133.21, 135.14, 139.15, 155.60, 159.42, 166.42, 192.24; Anal. calcd for $C_{24}H_{14}BrClO_4$: C, 59.84; H, 2.93; Found: C, 59.75; H, 2.82;

trans-2-4'-bromo-benzoyl-3-(2-chlorophenyl)-2H-furo[3,2-c]chromen-4(3H)-one (4e)

White powder, m.p 219-221º C, IR (KBr) cm^{-1}:2922, 2853, 1718, 1644, 1453, 1402, 1024, 755, 574; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.58 (CH, 1H, *J*= 5.2 Hz), 6.08 (CH, 1H, *J*= 5.2 Hz), 7.17-7.31 (m, 6H), 7.37 (m, 3H), 7.43 (d, *J*= 8 Hz, 1H), 7.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 48.82, 92.19, 105.12, 112.14, 117.28, 121.08, 122.36, 124.28, 127.28, 128.17, 128.57, 129.24, 130.58, 130.69, 132.54, 133.27, 134.41, 139.14, 155.62, 159.42, 166.38, 192.18; Anal. calcd for$C_{24}H_{14}BrClO_4$:C, 59.84; H, 2.93; Found: C, 59.72; H, 2.79;

trans-2-4'-bromo-benzoyl-3-(4-nitrophenyl)-2H-furo[3,2-c]chromen-4(3H)-one (4f) White powder, m.p 250-252 ºC, IR (KBr) cm^{-1}: 2932, 2834, 1734, 1636, 1432, 1025, 762, 535; ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 5.15 (CH, 1H, *J*= 4.8 Hz), 6.04 (CH, 1H, *J*= 4.8 Hz), 7.28 (m, 2H), 7.32 (t, *J* = 7.2 Hz, 1 H), 7.40 (m, 1H), 7.45 (d, *J* = 7.6 Hz, 2H), 7.49 (d, *J* = 7.6 Hz, 2H) 7.92- 8.12 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 48.05, 91.97, 104.35, 111.73, 117.28, 123.17, 124.48, 124.60, 128.75, 130.33, 130.65, 132.01, 132.57, 133.54, 146.47, 147.76, 155.48, 159.01, 166.38, 190.61; Anal. calcd for$C_{24}H_{14}BrNO_6$: C, 58.56; H, 2.87; N, 2.85;Found: C, 58.47; H, 2.79; N, 2.80;

trans-2-4'-bromo-benzoyl-3-(4-methylthiophenyl)-2H-furo[3,2-c]chromen-4(3H)-one (*4g*)

White powder, m.p 206-208 ºC, IR (KBr) cm^{-1}: 2925, 2829, 1724, 1647, 1406, 1027, 754, 538;^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.66 (s, CH_3, 3H), 4.77 (CH, 1H, d, *J*= 4.8 Hz), 6.07 (CH, 1H, d, *J*= 4.8 Hz), 7.16 (m, 4H), 7.30 (m, 1H), 7.41-7.87 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 15.68, 48.80, 92.04, 104.52, 112.03, 117.21, 120.94, 122.31, 124.24, 127.22, 127.99, 128.32, 130.53, 132.46, 133.25, 134.40, 139.17, 155.61, 159.42, 166.38, 192.03. Anal.calcd for $C_{25}H_{17}BrO_4S$: C, 60.86; H, 3.47; Found: C, 60.74; H, 3.54.

trans-2-4'-bromo-benzoyl-3-(4-bromophenyl)-2H-furo[3,2-c]chromen-4(3H)-one (**4h**)

White powder, m.p 256-258 ºC, IR (KBr) cm^{-1}:2919, 2821, 1718, 1644, 1402, 1024, 751, 535; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.86 (CH, 1H, *J* =5.2 Hz), 6.05 (CH, 1H, *J* = 5.2 Hz), 7.18 (m, 2H), 7.23 (m, 2H), 7.34 (m, 1H), 7.50-7.93 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 48.51, 92.28, 105.24, 112.24, 117.31, 121.25, 122.38, 124.21, 127.22, 128.51, 129.17, 130.57, 132.53, 133.21, 134.42, 139.14, 155.62, 159.43, 166.44, 192.16; Anal. calcd for $C_{24}H_{14}Br_2O_4$: C, 54.78; H, 2.68; Found: C, 54.61; H, 2.55.

trans-2-4'-bromo-benzoyl-3-(3-nitrophenyl)-2H-furo[3,2-c]chromen-4(3H)-one (4i)

White powder, m.p 250-252 ºC, IR (KBr) cm^{-1}: 2934, 2853, 1727, 1647, 1522, 1410, 747, 575;^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.17 (CH, 1H, *J*= 4.8 Hz), 6.07 (CH, 1H, *J*= 4.8 Hz), 7.34-7.39 (m, 2H), 7.42-7.47 (m, 4H), 7.92- 8.12 (m, 5H); 8.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 49.04, 93.50, 105.24, 112.28, 117.38, 121.29, 122.43, 124.33, 124.54, 127.37, 128.33, 128.39, 129.44, 131.73, 132.54, 133.35, 134.65, 139.16, 155.71, 159.48, 166.52, 193.10; Anal. calcd for$C_{24}H_{14}BrNO_6$: C, 58.56; H, 2.87; N, 2.85;Found: C, 58.47; H, 2.79; N, 2.80;

trans-2-4'-bromo-benzoyl-3-(4-methylphenyl)-2H-furo[3,2-c]chromen-4(3H)-one (4j)

White powder, m.p 204-206ºC, IR (KBr) cm^{-1}: 2932, 2862, 1721, 1646, 1458, 1403, 1025, 756, ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.45 (CH_3, 3H), 5.58 (CH, 1H, d, *J*= 5.4 Hz), 6.08 (CH, 1H, d, *J*= 5.4 Hz), 7.02-7.12 (m, 4H), 7.16-7.20 (m, 2H), 7.36-7.55 (m, 3H), 7.77-7.95 (m, 3H);^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.5, 48.65, 92.05, 104.52, 111.95, 117.18, 120.82, 124.22, 127.83, 128. 45,128.65, 129.14, 130.32, 132.42, 133.18, 134.32, 139.02, 155.55, 159.44, 166.30, 192.14; Anal.calcd for $C_{25}H_{17}BrO_4$: C, 65.09; H, 3.71; Found: C, 65.21; H, 3.85.

trans-2-4'-bromo-benzoyl-3-(2-fluorophenyl)-2H-furo[3,2-c]chromen-4(3H)-one (4k)

White powder, m.p 186-188º C, IR (KBr) cm^{-1}: 2922, 2853, 1718, 1644, 1453, 1402, 1024, 755, 574; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.50 (CH, 1H, *J* = 5.2 Hz), 6.18 (CH, 1H, *J* = 5.2 Hz), 7.27-7.51 (m, 6H), 7.47 (m, 3H), 7.53 (d, *J*= 7.6 Hz, 1H), 7.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 48.93, 92.31, 105.22, 113.02, 117.22, 121.18, 122.45, 124.20, 127.28, 128.17, 128.61, 129.31, 130.65, 131.72, 133.54, 133.71, 135.52, 139.21, 155.81, 159.52, 166.56, 192.30; Anal. calcd for $C_{24}H_{14}BrFO_4$: C, 61.96; H, 3.03; Found: C, 61.82; H, 2.92;

2-Benzoyl-3-p-chlorophenyl-2,3-dihydrofuro[3,2-c]chromen-4-one **(4l)**:

White powder, m.p 170-172º C, IR (KBr) cm^{-1}: 2924, 2855, 1717, 1643, 1454, 1406, 1024, 756, 572; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.85 (d, *J* = 5.2 Hz, 1H, CH), 6.06 (d, *J* = 5.2 Hz, 1H, CH), 7.20-7.89 (m, 13 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 48.72, 92.44, 104.92, 112.12, 117.14, 123.22, 124.23, 129.04, 129.10, 129.52, 133.12, 133.22, 134.15, 134.17, 134.60, 138.12, 155.43, 159.27, 166.58, 191.84; Anal. calcd for $C_{24}H_{15}ClO_4$: C, 71.56; H, 3.75; Found: C, 71.45; H, 3.69;

2-Benzoyl-3-3-fluorophenyl-2,3-dihydrofuro[3,2-c]chromen-4-one **(4m):**

White powder, m.p 210-212º C, IR (KBr) cm^{-1}: 3052, 1704, 1648, 1605, 1500, 1449, 1410, 1326, 887, 756; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.90 (d, *J* = 5.2 Hz, 1H, CH), 6.07 (d, *J* = 5.2 Hz, 1H, CH), 7.12-7.87 (m, 13 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 48.30, 92.21, 104.32, 111.83, 117.22, 122.52, 123.34, 124.44, 129.28, 129.32, 130.34, 133.21, 133.39, 133.45, 134.24, 134.75, 141.64, 148.96, 155.54, 159.18, 166.76, 191.48; Anal. calcd for $C_{24}H_{15}FO_4$: C, 74.61; H, 3.91; Found: : C, 74.55; H, 3.87;

trans-2-4'-bromo-benzoyl-3-phenyl-8-methoxy-2H-furo[3,2-c]chromen-4(3H)-one **(4o):**

White powder, m.p 218-220º C, IR (KBr) cm^{-1}: 3045, 1701, 1645, 1603, 1503, 1448, 1412, 1325, 882, 754; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.61 (s, 3H, OCH_3), 5.20 (d, *J* = 5.6 Hz, 1H, CH), 6.03 (d, *J* = 5.6 Hz, 1H, CH), 6.88-7.83 (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 48.62, 55.25, 92.36, 105.27, 112.29, 115.09, 121.29, 122.48, 123.99, 127.35, 128.76, 129.37, 131.15, 131.97, 133.34, 134.55, 138.78, 155.59, 159.48, 166.51, 192.08; Anal. Calcd for $C_{25}H_{17}BrO_5$: C, 62.91; H, 3.59; Found: C, 62.89; H, 3.61;

3. Results and Discussion

In the beginning, we prepared nanocrystalline $ZnZr_4(PO_4)_6$ ceramics. The particle size diameter (D) of the nano-$ZnZr_4(PO_4)_6$ has been calculated by the Debye–Scherrer equation ($D = K\lambda/\beta \cos\theta$), where β FWHM (full-width at half-maximum or half-width) is in radian and θ is the position of the maximum of the diffraction peak. K is the so-called shape factor, which usually takes a value of about 0.9, and λ is the X-ray wavelength. Fig.1 shows the XRD spectra of nano-$ZnZr_4(PO_4)_6$. According to the Debye–Scherrer equation, the average particle sizes of the as-synthesized nano-$ZnZr_4(PO_4)_6$ were calculated and the results show that nano-$ZnZr_4(PO_4)_6$ was obtained with an average diameter of 70-75 nm as confirmed by XRD analysis. In order to investigate the morphology and particle size of nano-$ZnZr_4(PO_4)_6$, FE-SEM image of nano-$ZnZr_4(PO_4)_6$ was presented in Fig. 2. The FE-SEM image shows particles with diameters in the range of nanometers.

Fig. 1.

Fig. 2.

As shown in Figures 3, the EDS analysis was carried out for nano-$ZnZr_4(PO_4)_6$. The EDS spectrum has indicated that only Zn, Zr, P and O elements for $ZnZr_4(PO_4)_6$ which it supports XRD results.

Fig. 3.

We focused on systematic evaluation of different catalysts for the model reaction of 2,4′-dibromoacetophenone, pyridine, benzaldehyde**,** 4-hydroxycoumarin as a model reaction. The model reactions were carried out in the presence of various catalysts, such as morpholine, ZnO, ZnS, ZrO_2 and nano-$ZnZr_4(PO_4)_6$. When the reaction was carried out using ZrO_2 and nano-$ZnZr_4(PO_4)_6$ as the catalyst, the product could be obtained in a moderate to good yield. Nanoparticles exhibit good catalytic activity owing to their large number of active sites which are mainly responsible for their catalytic activity. The best results were obtained under microwave irradiation (400 W) in ethanol and the reaction gave satisfying results in the presence of nano-$ZnZr_4(PO_4)_6$ as catalyst. When 1, 2 and 3 mol% of nano-$ZnZr_4(PO_4)_6$ were used; the yields were 78%, 85% and 85%, respectively. Consequently, 2 mol% of nano-$ZnZr_4(PO_4)_6$ were expedient and excessive amount of nano-$ZnZr_4(PO_4)_6$ did not change the yields, significantly (Table 1). When the catalysis was performed under microwave irradiation, the reaction rate

increased considerably (Entry 10). In this research, microwave irradiation is used as a green and complementary technique for preparation of furocoumarins.

Table 1.

With these hopeful results in hand, we turned to investigate the scope of the reaction by various aromatic aldehydes, acetophenones and coumarines as substrates under the optimized reaction conditions (Table 2). It was shown that aromatic aldehydes with electron-withdrawing groups reacted faster than those with electron-releasing groups. Meanwhile, it has been observed that better yields are obtained with substrates having electron-withdrawing groups. The highest yields of furo[3,2-c]coumarins were obtained by the electron-withdrawing para-nitro and para-chloro groups as substituent for aromatic aldehydes (Table 2, entries 4 and 6). Although other electron-withdrawing substituted aromatic aldehydes were resulted in good yield (entries 5 and 9 in Table 2) but, due to steric effects, yields are lower than para-position.

Table 2.

In the recycling procedure of nanocrystalline $ZnZr_4(PO_4)_6$ ceramics, hot CH_3OH was added to dilute the reaction mixture after terminating the reaction. The catalyst was insoluble in the solvent and was separated by filtering. The recycling ability of the catalyst was tested for nine runs, providing almost similar yields of the desired product.

Fig. 4.

A plausible mechanism for the synthesis of furo[3,2-c]coumarins using nano-$ZnZr_4(PO_4)_6$ is shown in Scheme 2. Firstly, we supposed that the reaction occurs *via* a Knoevenagel condensation between benzaldehyde and 4-hydroxycoumarin to form the intermediate **I** on the active sites of nano-$ZnZr_4(PO_4)_6$ which are mainly responsible for their catalytic activity. Then, the Michael addition of pyridinium ylide with enones affords the zwitterionic intermediate and followed by cyclization affords the titled product. The final step is a classic intramolecular S_N2 substitution reaction. The

stereochemistry of the S_N2 reaction necessitated nucleophilicenolate attack from the back side of the electrophilic carbon atom bearing the leaving pyridinium group, which afterward assumes 2-benzoyl and 3-aryl groups in a stereo-chemical opposite position for the sake of steric hindrance in transition states. Thus, only trans isomeric 2,3-dihydrofuran is obtained as only product [13]. In this proposed reaction mechanism pyridine plays very important role. It acts as a nucleophilic tertiary amine to form zwitterionic salt and acts as a good leaving group to finish the intramolecular substitution reaction. In this mechanism the nano-$ZnZr_4(PO_4)_6$ act as Lewis solid acid and activate the C=O group for better reaction with nucleophiles. The solid catalysts absorb microwave irradiation, thus they can serve as an internal heat source for the reaction.

The observed stereoselective formation of trans-2-benzoyl-3-(aryl)-2H-furo[3,2-c]chromen-4(3H)-ones is in agreement with the lower heat of formation of *trans*-isomer, which is more stable than its cis isomer, as estimated using PM3 calculations [10]. The structures of the prepared *trans*-2-benzoyl-3-(aryl)-2*H*-furo[3,2-c]chromen-4(3*H*)-ones were fully characterized by ^{1}H and ^{13}C NMR and IR spectra and elemental analysis. For example, in the ^{1}H NMR spectra of **4a,** the two protons at 2,3-position of dihydrofuran ring display two doublets at 4.82 and 6.11 ppm with the vicinal coupling constant J = 5.2 Hz. The similar peak pattern and coupling constant less than 6.0 Hz were also seen in other ^{1}H NMR spectra of prepared furo[3,2-c]chromen derivatives. It has been established that in *cis*-2,3-dihydrofuran the vicinal coupling constant of the two methine protons J= 7-10 Hz, while in *trans*-2,3-dihydrofuran vicinal coupling constant J= 4 - 7Hz [14].

Scheme 2.

4. Conclusion

In conclusion, we have developed a flexible, green and highly efficient protocol for the synthesis of *trans*-2-benzoyl-3-(aryl)-2H-furo[3,2-c]chromen-4(3H)-ones catalyzed by nano-$ZnZr_4(PO_4)_6$. Present method tolerates most of the substrates, and the catalyst can be recycled at least nine times without considerable loss of activity. The advantages of this method are the use of an efficient catalyst, using of microwave as clean method, recoverability of the catalyst, little catalyst loading, low reaction times and easy separation of products. The present work demonstrates the advantages of microwave irradiation-assisted heterogeneous catalysis in the synthesis of furocoumarins; compounds that generate great attention in many applications, particularly in medicinal chemistry and drug discovery.

supporting information

Please view the supplementary material, available online, for complete experimental details.

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Table 1. Optimization of the model reaction using various catalysts [a]

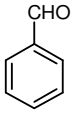
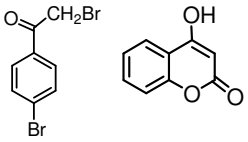
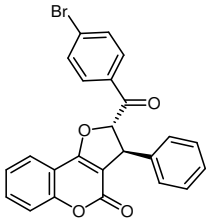
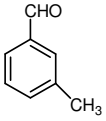
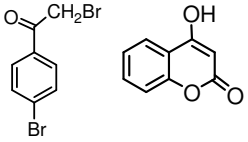
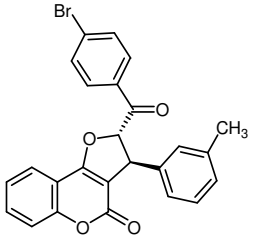
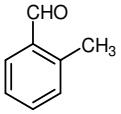
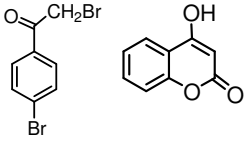
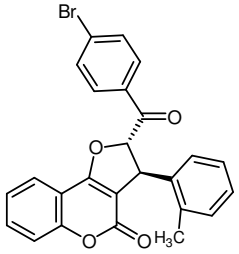
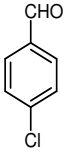
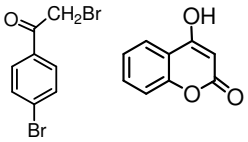
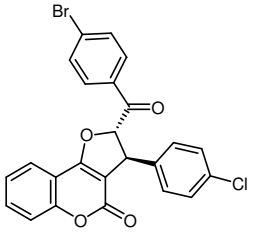
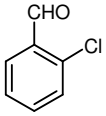
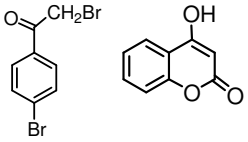
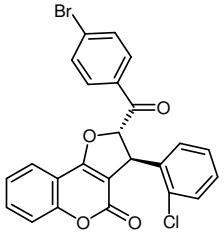
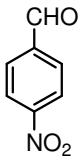
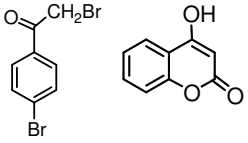
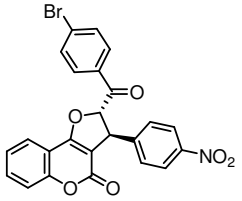
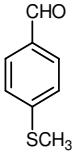
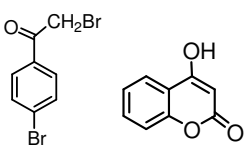
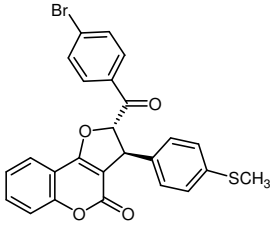
Entry	Solvent (Conditions)	Catalyst (mol%)	Time (min)	Yield[b]%
1	EtOH (reflux)	Morpholine (7)	200	35
2	CH_3CN (reflux)	ZnO (5)	180	30
3	H_2O (reflux)	ZnS (10)	200	15
4	EtOH (reflux)	ZnS (5)	150	35
5	EtOH (reflux)	ZrO_2 (4)	150	40
6	DMF (reflux)	nano-$ZnZr_4(PO_4)_6$ (2)	120	45
7	CH_3CN (reflux)	nano-$ZnZr_4(PO_4)_6$ (2)	120	55
8	EtOH (reflux)	nano-$ZnZr_4(PO_4)_6$ (2)	120	60
9	EtOH (MWI:[c] 300 W)	nano-$ZnZr_4(PO_4)_6$ (1)	10	78
10	**EtOH (MWI: 400 W)**	**nano-$ZnZr_4(PO_4)_6$ (2)**	**10**	**85**
11	EtOH (MWI: 500 W)	nano-$ZnZr_4(PO_4)_6$ (3)	10	85
12	CH_3CN (MWI: 500 W)	nano-$ZnZr_4(PO_4)_6$ (3)	10	80

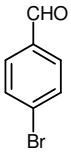
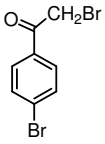
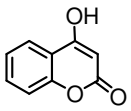
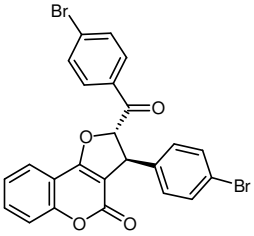
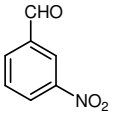
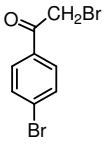
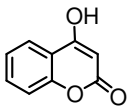
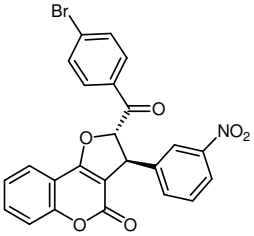
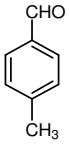
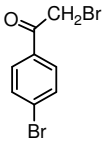
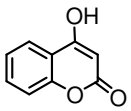
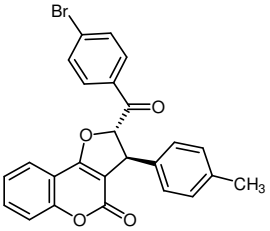
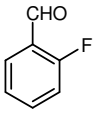
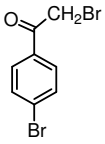
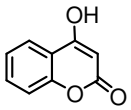
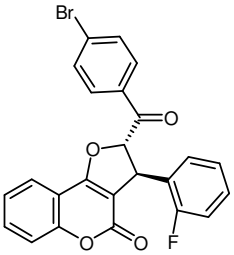
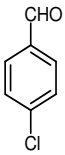
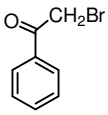
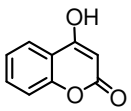
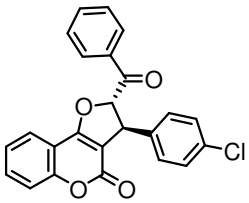
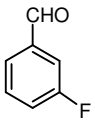
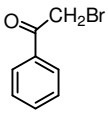
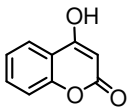
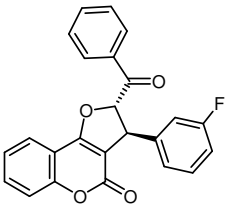
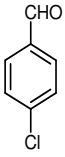
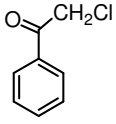
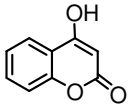
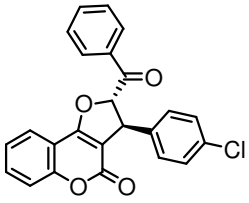
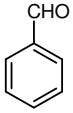
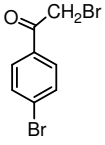
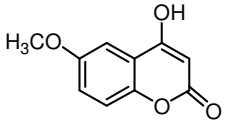
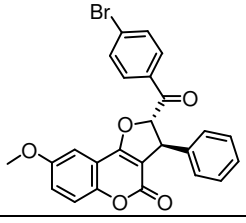
[a] 2,4′-dibromoacetophenone (1 mmol), benzaldehyde (1 mmol), 4-hydroxycoumarin (1 mmol),

[b] Isolated yield.

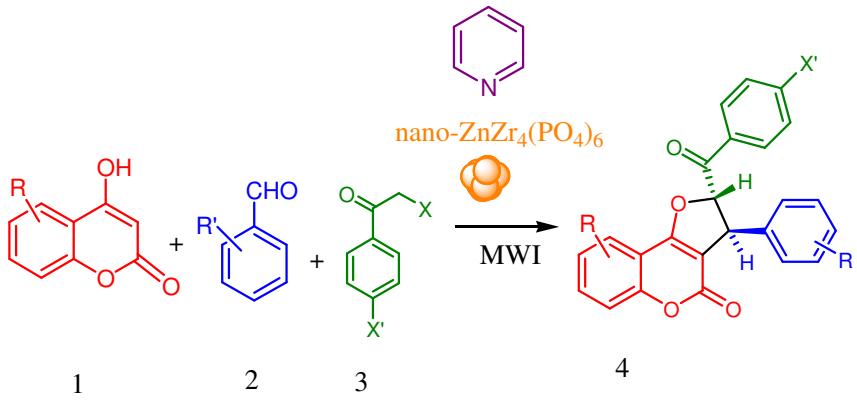
[c] (MWI): MicroWave Irradiation

Table 2. Synthesis of furo[3,2-c]coumarins using nano-$ZnZr_4(PO_4)_6$ (2 mol%) under microwave irradiation (400 W)

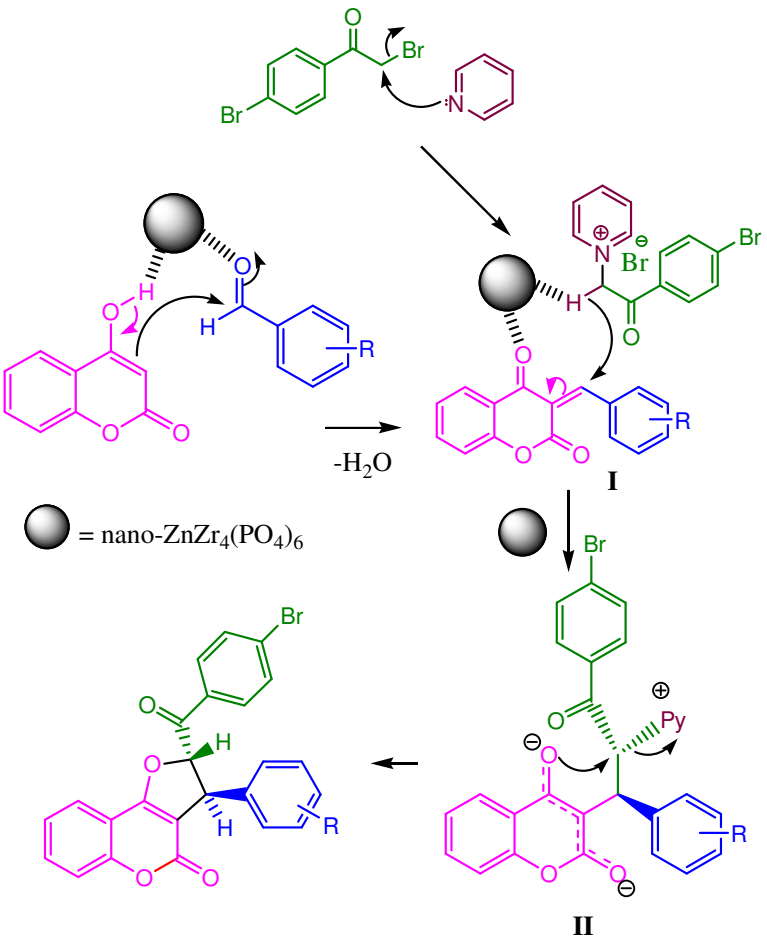
Entry	Aldehyde	3a-c	Product	Product	Time (min)	Yield[a] %	m.p °C
1			**4a**		10	85	243-244
2			**4b**		15	76	222-224
3			**4c**		20	75	171-173
4			**4d**		10	88	250-252
5			**4e**		10	85	219-221
6			**4f**		10	89	250-252
7			**4g**		20	73	206-208

8				**4h**		10	88	256-258
9				**4i**		10	86	250-252
10				**4j**		15	80	204-206
11				**4k**		10	86	186-188
12				**4l**		15	83	170-172
13				**4m**		20	81	210-212
14				**4n**		20	75	170-172
15				**4o**		15	83	218-220

[a] Isolated yield



Scheme 1. One-pot syntheses of furo[3,2-c]coumarins in the presence of nano-$ZnZr_4(PO_4)_6$ under microwave irradiation



Scheme 2.Possible mechanism for the synthesis of furo[3,2-c]coumarins in the presence of nano-$ZnZr_4(PO_4)_6$

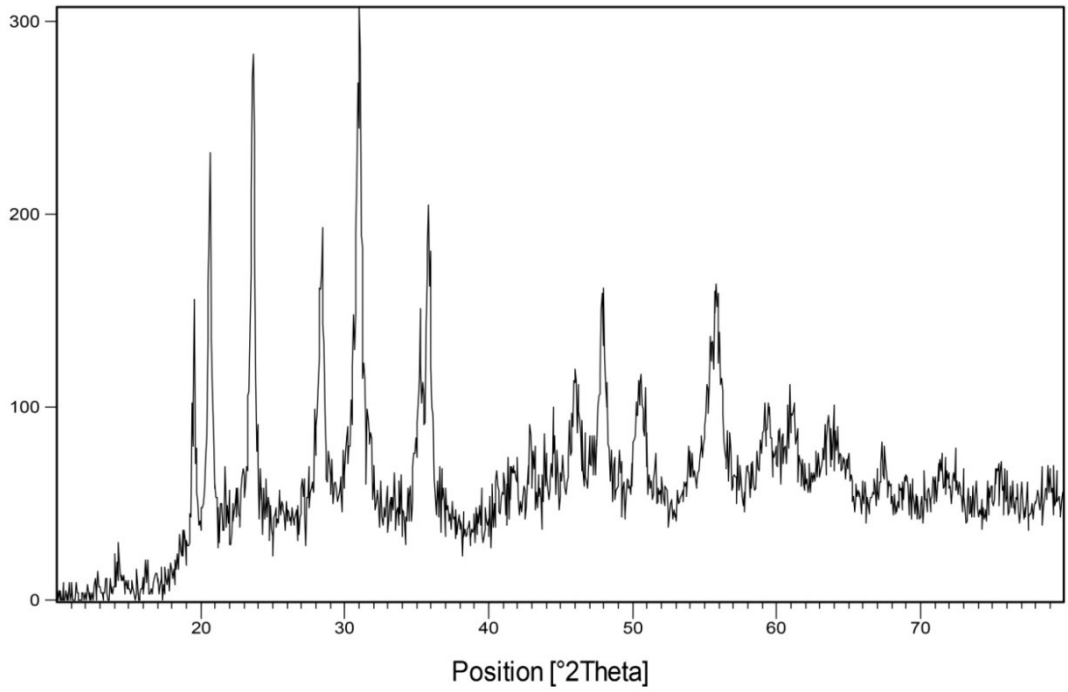


Fig. 1. The XRD pattern of nano-$ZnZr_4(PO_4)_6$

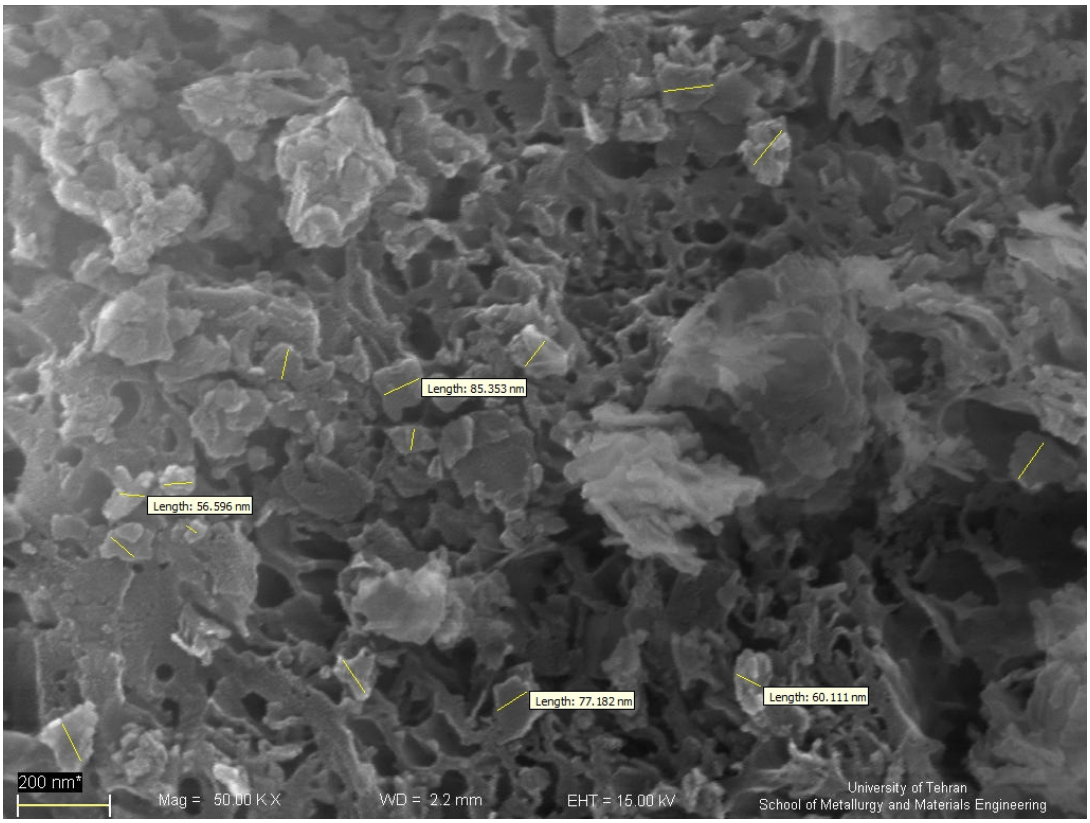


Fig. 2. FE-SEM images of nano-$ZnZr_4(PO_4)_6$

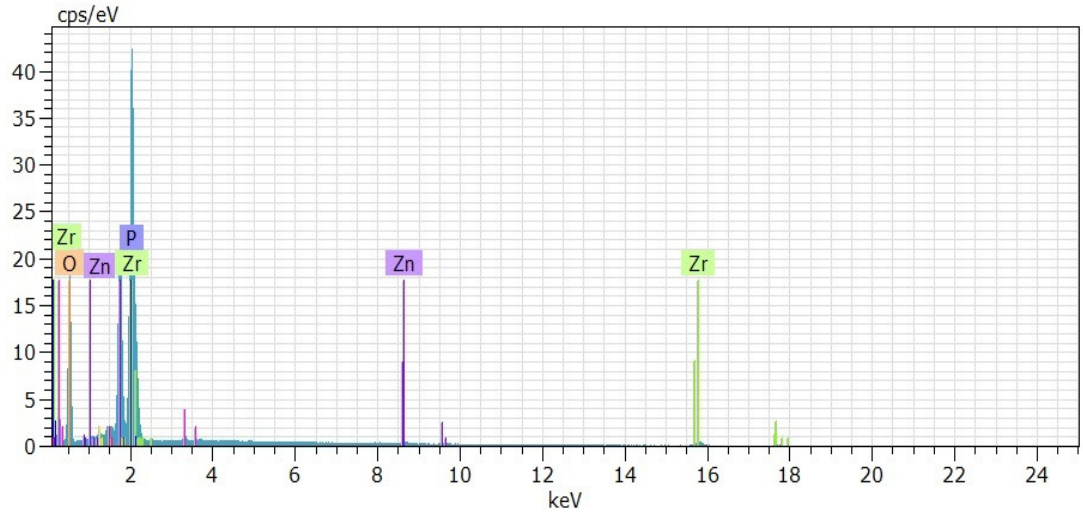


Fig. 3. EDS analysis of nano-$ZnZr_4(PO_4)_6$

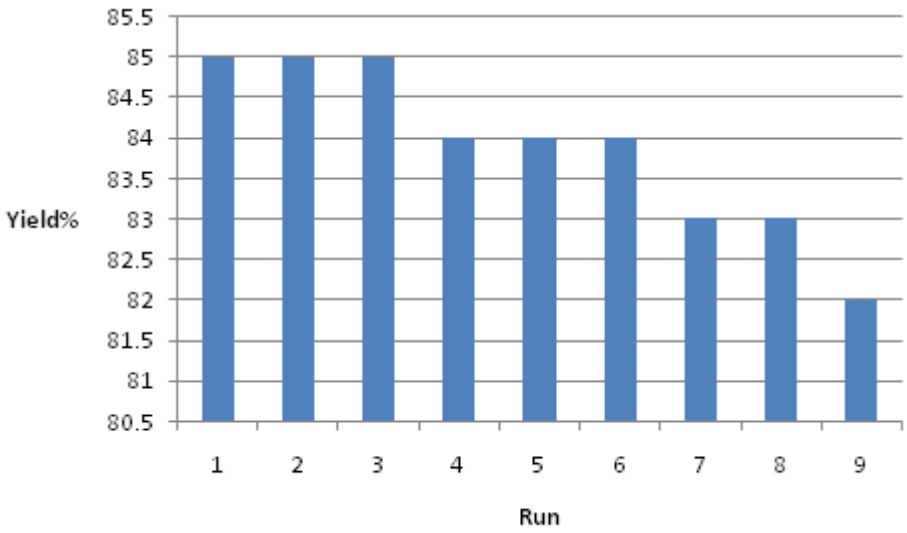


Fig. 4. Recycling of the nano-$ZnZr_4(PO_4)_6$