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Three-component, One-pot Synthesis of Dihydropyrano[3,2-*c*]chromenes in Aqueous Medium in the Presence of Nano-silica Supported 1,5-Diazabicyclo(4.3.0)non-5-en

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In this research, a high efficient, simply and rapid method was applied for the synthesis of dihydropyrano[3,2-*c*]chromene derivatives by one-pot, three-component condensation of aldehydes, malononitrile and 4-hydroxycoumarin in H_2O/ethanol (1:1 *v/v*) under reflux conditions. This reaction was run by using nano-silica supported 1,5-diazabicyclo(4.3.0)non-5-en (DBN) which has been abbreviated as nano-SiO_2/DBN under aqueous condition. The nano-SiO_2/DBN catalyst was synthesized by reaction between silica chloride and DBN. The main advantages of this procedure are high yields, short reaction times and easy work-up. Furthermore, the catalyst could be reused for five times.

Keywords: Dihydropyrano[3,2-*c*]chromene, 4-Hydroxycoumarin, 1,5-Diazabicyclo(4.3.0)non-5-en, Nano-Silica, nano-SiO_2/DBN, Aqueous medium

INTRODUCTION

Dihydropyrano[3,2,*c*]chromene derivatives are one of the most important classes of heterocyclic compounds which have pharmacological and biological properties, such as anticancer [1], anticoagulant [2], antimicrobial [3], inhibition of cell proliferation and induction of apoptosis in K562 human leukemia cells [4], diuretic, analgesic, myorelaxant [5], antitumor [6] and antiHIV [7]. In addition, these compounds have benefits for the therapy of sickness, including amyotrophic lateral sclerosis, Huntington's disease, Alzheimer's disease, Parkinson's disease, AIDS-associated dementia, Schizophrenia, Down's syndrome, myoclonus [8], antimalarial [9], sex-hormonal activity [10], anti-viral [11], anti-inflammatory [12], TNF-α inhibitor [13], antiproliferative [14], antihelminthic [15], and anticonvulsant [16]. Chromene derivatives are found in many natural products such as calanolides, calophyllolide, and calanone [17]. Some pharmacologically and biologically active dihydropyrano[3,2-*c*]chromenes are shown in Fig. 1.

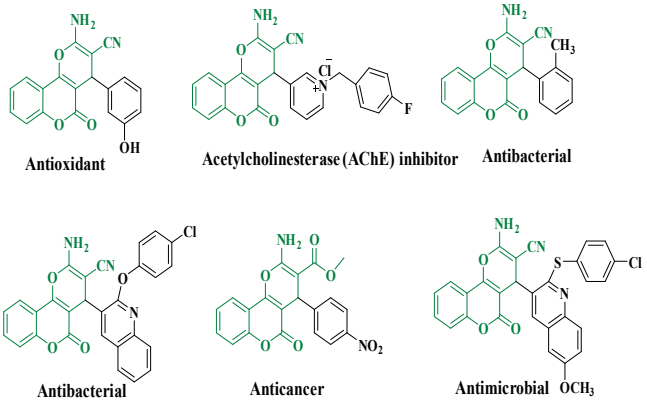

Fig. 1. Biologically active dihydropyrano[3,2-*c*]chromenes.

Multi-component reactions (MCRs) have significant role in organic chemistry due to some merits like selectivity, synthetic convergence, high atom economy, simplicity, short

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reaction time, facility of workup, synthetic efficiency and high yield of products [18,19]. An efficient way for the synthesis of heterocyclic compounds is using multi-component reactions, which have great value in design of biologically new active compounds [18,20-22]. In recent studies, several methods for the synthesis of these heterocyclic compounds have been stated with various catalysts such as $H_6[P_2W_{18}O_{62}].18H_2O$ [23], CH_3COONH_4 [24], TBAB [25], DBU [26], piperidine [27], TUD [28], potassium phthalimide [29], morpholine [30], SDS [31], DAHP [32], CF_3COONH_4 [33], nano ZnO [34], MgO [35], TMGT [36], pyridine [37], [bmim]OH [38], KF-montmorillonite [39], heteropolyacids (HPA) [40], *β*-CD [41], PS-PTSA [42], P4VPy [43], nano Al_2O_3 [44], (S)-proline [32] and DABCO [45].

In this research a practical, simple and inexpensive procedure for the synthesis of dihydropyrano[3,2-c]chromene derivatives is reported by the reaction of aldehydes, malononitrile and 4-hydroxycoumarin in the presence of catalytic amount of nano-silica supported 1,5-diazabicyclo(4.3.0)non-5-en (Nano-SiO_2/DBN) [46]. Moreover, the amount of catalyst which has been used in the reaction and its effect on the product yields, as well as the ability to recovery have been studied. Inexpensive and readily available catalyst, easy work-up, high yield of the products, usage of environmentally benign solvents, short reaction times and simplicity of experimental procedure are some advantages of this procedure.

RESULTS AND DISCUSSION

The nano-SiO_2/DBN, is determined by various methods such as Fourier Transform Infrared Spectroscopy (FT-IR), Field Emission Scanning Electron Microscope (FE-SEM), X-ray diffractometer (XRD), Thermo Gravimetric Analysis (TGA), BET surface area, and Energy Dispersive X-ray Spectroscopy (EDS).

The FT-IR spectra of the synthesized materials was indicated in (Figs. 2a-c). There is an absorption band at 3397 cm^{-1} which is shown the SiO–H stretching vibration (Fig. 2d). Other absorptions are as follows: 1652 cm^{-1} for the C=N stretching vibration, 1056 cm^{-1} for Si–O stretching vibration and 796 cm^{-1} due to the Si–O–Si bending vibrational mode (Fig. 2d). In order to distinguished the percentage of elements in synthesized nano-catalyst, Energy-dispersive X-ray spectroscopy (EDS) was used (Fig. 3). The percentage of C, N, O, Si and Cl in nano-SiO_2/DBN was 10.75, 4.88, 47.38, 36.48 and 0.25 respectively.

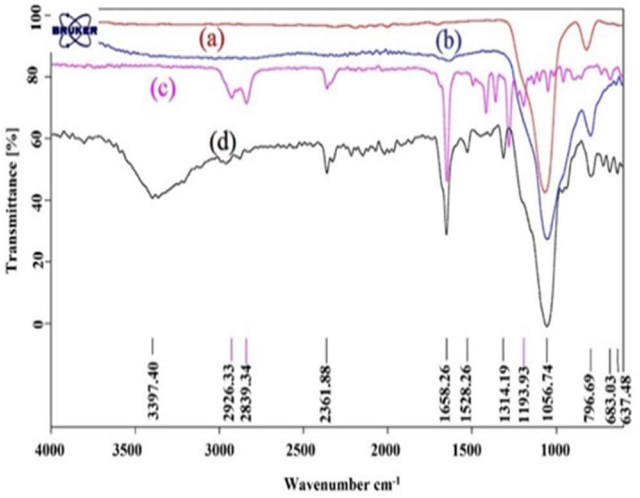


Fig. 2. FT-IR spectra of a) Nano-SiO_2, b) Nano-silica chloride, c) DBN, d) Nano-SiO_2/DBN.

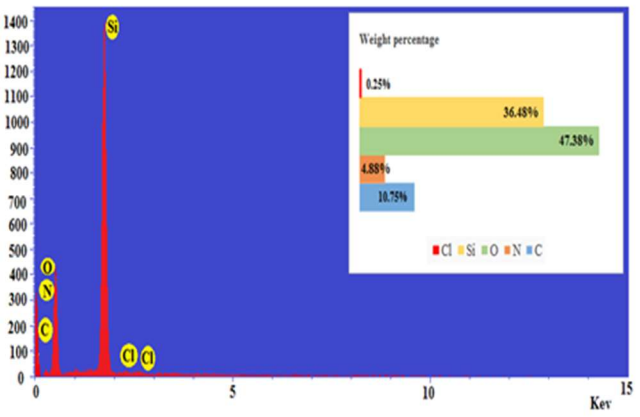


Fig. 3. The EDX spectra of Nano-SiO_2/DBN.

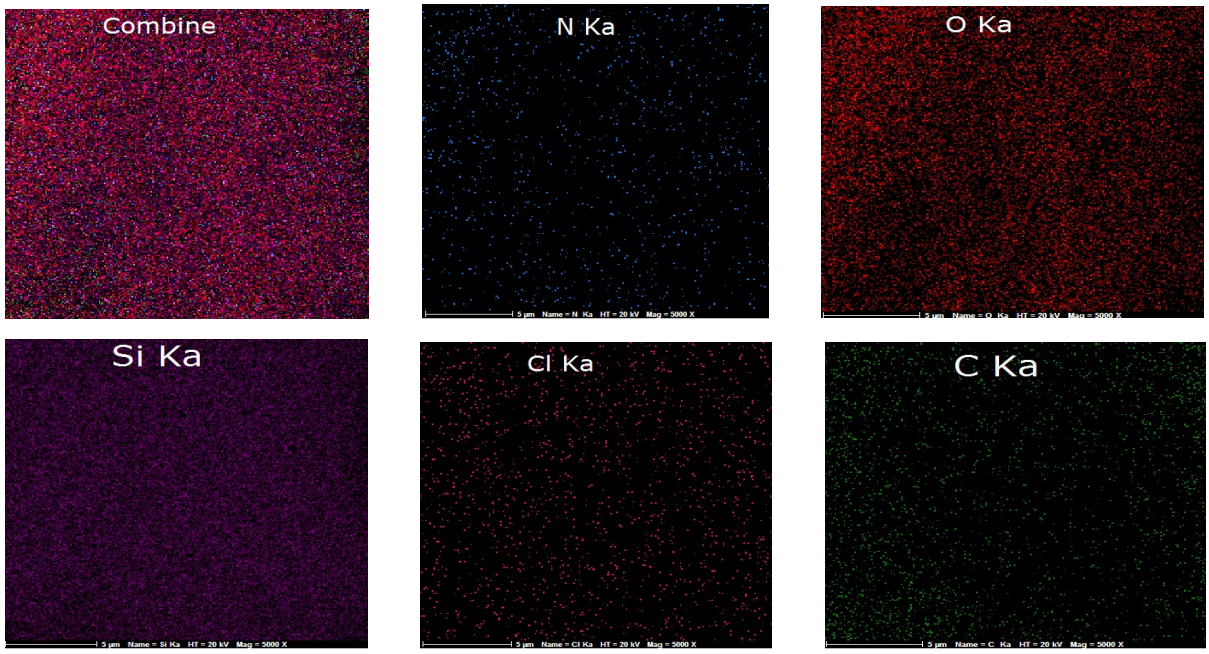


Fig. 4. EDX-map of elements in the structure of Nano-SiO_2/DBN.

By usage of The EDX-map (Fig. 4), homogenous distribution of elements in catalyst can be seen. The particle size of nano-SiO_2/DBN was found to be less than 50 nm by using field emission scanning electron microscopy (FESEM) (Fig. 5).

The stability of the nano-SiO_2/DBN can be used up to 120 °C., this property is shown in Fig. 6A by using TGA method. The weight loss (4.2%) can be seen under 100 °C. The reason is because of catalyst moisture. Although, the major decomposition take places at 165-450 °C (20.7%). Nano-SiO_2/DBN has shown significantly high thermal stability at 800 °C.

The XRD Patterns of nano-SiO_2 and nano-SiO_2/DBN are shown in the range of 10-80° Fig. 6B. A broad peak (Fig. 6B (a)) is noticed at $2\theta = 23°$, displaying that the SiO_2 is amorphous. While, the diffraction pattern of the nano-SiO_2/DBN (Fig. 6B (b)) showed peak at $2\theta = 23.525°$ with FWHM = 2.3616. According to Scherrer equation, the particle size of catalyst is 3.4 nm. Figure 7 shows (A) BJH plot, (B) BET (Brunauer-Emmett-Teller) plot, (C) t-plot, (D) Langmuir plot and (E) Adsorption / desorption isotherm of nano-SiO_2/DBN. The obtained data of BET, Langmuir, t and BJH plots were summerized in Table 1.

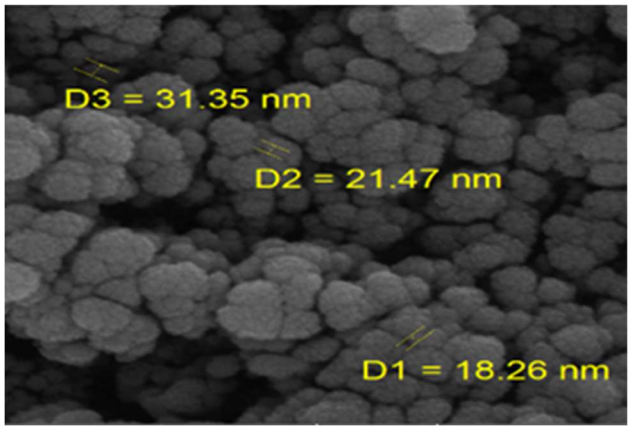


Fig. 5. FESEM images of Nano-SiO_2/DBN.

EXPERIMENTAL

General

Whole reagents and solvents were procured from Merck,

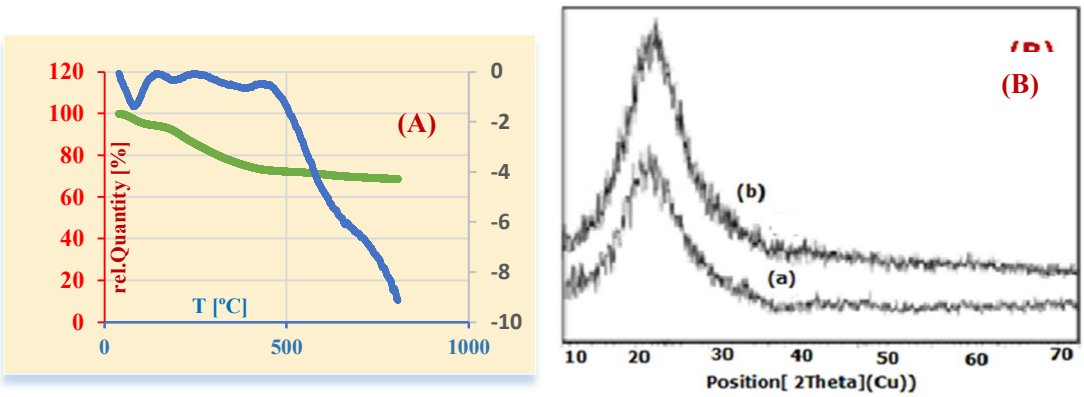


Fig. 6. (A) TGA patterns of Nano-SiO_2/DBN and (B) XDR patterns of a) Nano-SiO_2 and b) Nano-SiO_2/DBN.

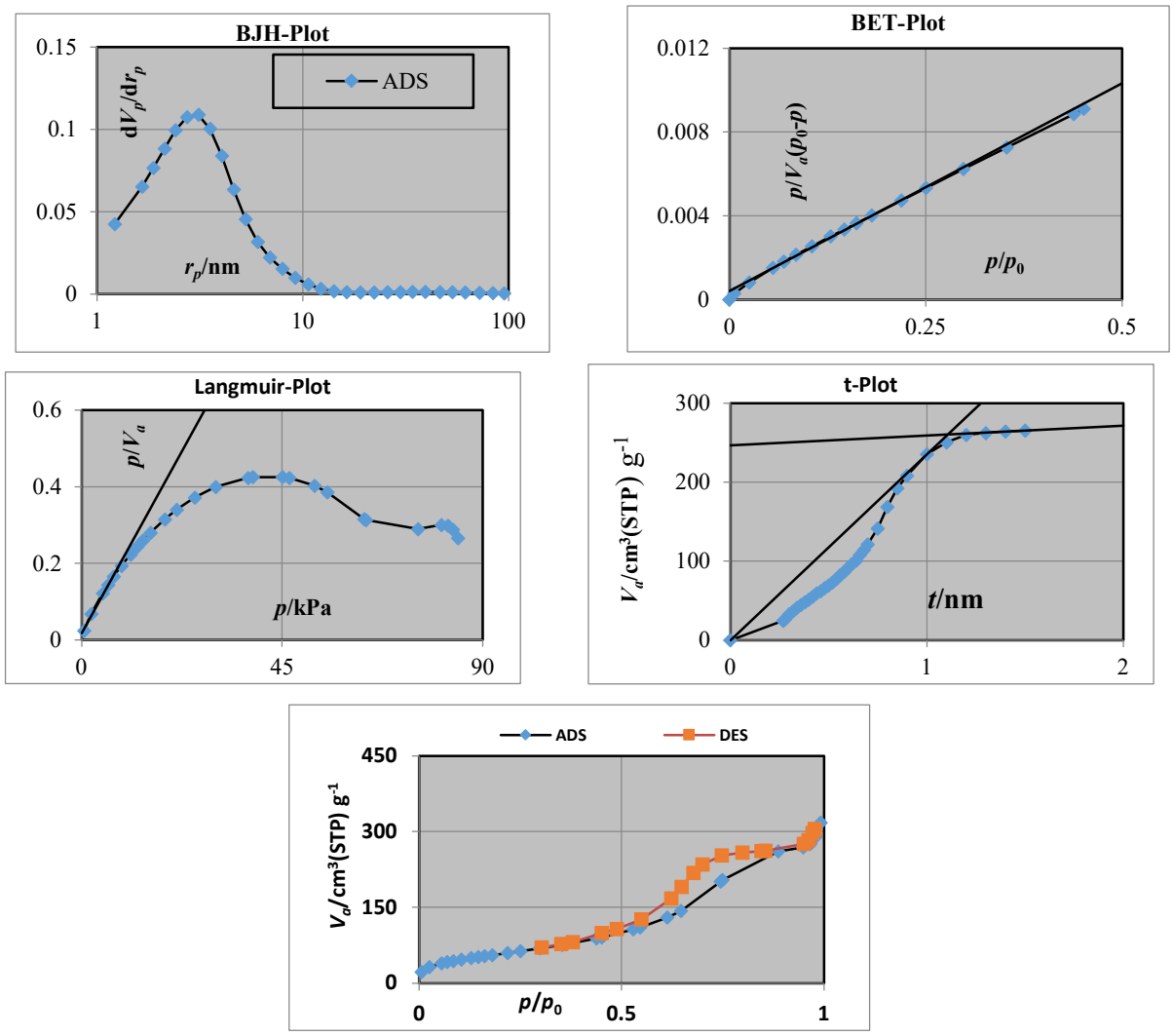


Fig. 7. (A) BJH plot, (B) BET (Brunauer-Emmett-Teller) plot, (C) t-plot, (D) Langmuir plot and (E) Adsorption/desorption isotherm of nano-SiO_2/DBN.

Table 1. The Summerized Data of BET, Langmuir, t and BJH Plots

BET plot		
V_m	49.439	(cm^3 (STP) g^{-1})
$a_{s,BET}$	215.18	(m^2 g^{-1})
C	48.241	
Total pore volume ($p/p_0 = 0.990$)	0.4823	(cm^3 g^{-1})
Mean pore diameter	8.966	(nm)
Langmuir plot		
Vm	47.372	(cm^3 (STP) g^{-1})
$a_{s,Lang}$	206.18	(m^2 g^{-1})
B	1.1678	
t-plot		
Plot data	Adsorption branch	
a_1	362.85	(m^2 g^{-1})
V_1	0	(cm^3 g^{-1})
a_2	19.303	(m^2 g^{-1})
V_2	0.3824	(cm^3 g^{-1})
2t	2.2126	(nm)
BJH plot		
Plot data	Adsorption branch	
V_p	0.504	(cm^3 g^{-1})
$r_{p,peak}$ (*Area*)	3.1	(nm)
a_p	290.06	(m^2 g^{-1})

Aldrich and fluka chemical companies. Fourier transform infrared spectroscopy (FT-IR) (ATR or KBr pellets) was run on a Bruker, Eqinox 55 spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were record at Bruker (DRX-400 Avance) in DMSO-d_6 as the solvent. Melting points were recorded on a Buchi B- 540 B. V. CHI apparatus.

General Procedure for Synthesis of Nano-SiO_2/DBN

Nano-SiO_2/DBN was synthesized in two steps. In the first step, thionyl chloride (40 ml) and commercial nano-silica gel (10 g) were mixed in a flask (250 ml) and stirred for 48 h under reflux condition to form nano-silica chloride. After completion, the mixture was filtered and the residue was rinsed via dichloromethane. In the next step, dried nano-silica chloride (1 g), reacted with DBN (1.5 ml) in *n-hexane* (10 ml) under reflux condition. After 15 h reflux, the mixture was cooled, filtrated and washed three times by usage of *n*-hexane. Ultimately, the dried nano-SiO_2/DBN catalyst was stored at room temperature.

General Procedure for Synthesis of Dihydropyrano[3,2-*c*]chromene Derivatives

A mixture of 4-hydroxycoumarine (1 mmol), aldehyde

(1 mmol), malononitrile (1 mmol) and nano-SiO_2/DBN (0.04 g) was added to in a round bottom flask and then the mixture was stirred magnetically in 5 ml H_2O/EtOH (1:1) under refluxed conditions. The progress of the reaction was controlled by TLC (*n*-hexane-ethyl acetate, 3:1). After completion of the reaction, the catalyst was separated by hot filtration. The filtrate was cooled until the solid products were appeared. The crude products were recrystallized in EtOH/H_2O.

Spectral Data for Selected Compounds

2-Amino-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (4a). White Solid, Melting point: 256-258 °C, FT-IR (ATR)/υ (cm^{-1}): 3371, 3284, 3176, 2196, 1706, 1671, 1604. ^{1}HNMR (500 MHz, DMSO-d_6) δ (ppm): 4.45 (s, 1H, CH), 7.22-7.33 (m, 5H, Ar-H), 7.42-7.49 (m, 4H, Ar-H, NH_2), 7.71 (t, *J* = 8 Hz, 1H, Ar-H), 7.91 (d, *J* = 8 Hz, 1H, Ar-H). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 37.00, 57.94, 103.99, 112.95, 116.61, 119.28, 122.38, 122.56, 124.77, 127.13, 127.65, 128.53, 132.83, 133.04, 143.36, 152.13, 153.42, 157.98, 159.55.

2-Amino-4-(4-chlorophenyl)-5-oxo-4,5-dihydro-pyrano[3,2-*c*]chromene-3-carbonitrile (4b). White Solid, Melting point: 261-263 ºC, FT-IR (ATR)/υ (cm^{-1}): 3401, 3320, 3195, 2201, 1700, 1668, 1605; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 4.73 (s, 1H, CH), 7.46 (d, *J* = 8 Hz, 1H, Ar-H), 7.51 (t, *J* = 7.5, 1H, Ar-H), 7.56 (s, 1H, NH_2), 7.64 (t, *J* = 8 Hz, 1H, Ar-H), 7.73 (t, *J* = 8 Hz, 1H, Ar-H), 7.82 (d, *J* = 8 Hz, 1H, Ar-H), 7.92 (d, *J* = 7.5 Hz, 1H, Ar-H), 8.11-8.14 (m, 2H, Ar-H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 36.70, 56.97, 102.93, 113.01, 116.55, 119.04, 122.31, 122.57, 125.02, 130.26, 132.73, 134.70, 145.56,147.65, 147.90, 152.33, 153.94, 158.20, 159.67.

2-Amino-4-(2-chlorophenyl)-5-oxo-4,5-dihydro-pyrano[3,2-*c*]chromene-3-carbonitrile (4c). White Solid, Melting point: 275-277 ºC, FT-IR (ATR)/υ (cm^{-1}): 3392, 3281, 3175, 2200, 1704, 1671, 1601; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 4.98 (s, 1H, CH), 7.26-7.33 (m, 3H, Ar-H), 7.40-7.52 (m, 5H, Ar-H, NH_2), 7.65-7.74 (m, 2H, Ar-H), 7.90-7.92 (dd, J_1 = 1Hz, J_2 = 7.5 Hz, 1H, Ar-H); ^{13}C NMR (125 MHz, DMSO-d_6) δ(ppm): 56.44, 86.64, 102.92, 112.21, 112.82, 113.47, 118.84, 127.72, 128.82, 129.63, 132.40, 134.28, 140.21, 152.20, 154.04, 158.03, 158.13, 159.42.

2-Amino-4-(2,6-dichlorophenyl)-5-oxo-4,5-dihydro-pyrano[3,2-*c*]chromene-3-carbonitrile (4d). White Solid, Melting point: 274-277 ºC, FT-IR (ATR)/υ (cm^{-1}): 3415, 3276, 3170, 2200, 1703, 1669, 1633. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 5.52 (s, 1H, CH), 7.29-7.38 (m, 2H, Ar-H), 7.46-7.52 (m, 5H, Ar-H, NH_2), 7.74 (t, *J* = 8.4 Hz, 1H, Ar-H), 7.88 (d, *J* = 7.5 Hz, 1H, Ar-H).

2-Amino-4-(4-nitrophenyl)-5-oxo-4,5-dihydropyrano [3,2-*c*]chromene-3-carbonitrile (4e). Pale yellow solid, Melting point: 261-263 ºC, FT-IR (ATR)/υ (cm^{-1}): 3429, 3369, 3334, 2195, 1716, 1672, 1603. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 4.67 (s, 1H, CH), 8.17 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.91 (d, *J* = 7.2 Hz, 1H, Ar-H), 7.74 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.46-4.60 (m, 6H, Ar-H).

2-Amino-4-(3-nitrophenyl)-5-oxo-4,5-dihydropyrano [3,2-*c*]chromene-3-carbonitrile (4f). Yellow solid, Melting point: 265-267 ºC, FT-IR (ATR)/υ (cm^{-1}): 3401, 3317, 3191, 2202, 1700, 1668, 1605, 1527, 1380, 1207, 1112, 1055, 956, 733; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 4.73 (s, 1H, CH),7.45-7.52 (m, 2H, Ar-H), 7.57 (s, 2H, NH_2), 7.61-7.65 (m, 1H, Ar-H), 7.72 (td, J_1 = 1.6 Hz, J_2 = 8Hz, 1H, Ar-H), 7.81 (d, *J* = 8 Hz, 1H, Ar-H), 7.92 (dd, J_1 = 1.6 Hz, J_2 = 8 Hz, 1H, Ar-H), 8.11 (d, *J* = 8 Hz, 2H, Ar-H).

2-Amino-4-(2-nitrophenyl)-5-oxo-4,5-dihydropyrano [3,2-*c*]chromene-3-carbonitrile (4g). Pale yellow solid, Melting point: 255-257 ºC, FT-IR (ATR)/υ (cm^{-1}): 3398, 3287, 3183, 2195, 1700, 1670, 1602; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 5.24 (s, 1H), 7.44-7.57 (m, 6H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.73 (dt, *J* = 7.5 Hz, 1H), 7.90 (d, *J* = 8 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d6) *δ* (ppm) 31.56, 56.02, 103.32, 112.84, 116.67, 118.72, 122.48, 123.90, 124.08, 124.87, 131.29, 133.48, 137.36, 149.19, 152.18, 153.59, 158.61, 159.74.

2-Amino-4-(4-bromophenyl)-5-oxo-4,5-dihydro-

pyrano[3,2-*c*]chromene-3-carbonitrile (4h). White Solid, Melting point: 257-259 ºC. FT-IR (ATR)/υ (cm^{-1}): 3382, 3292, 3186, 2189, 1707, 1672, 1604; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 4.46 (s, 1H, CH), 7.45-7.51 (m, 6H, Ar-H), 7.73 (t, J = 8.4 Hz, 1H, Ar-H), 7.87 (d, J = 8 Hz, 2H, Ar-H).

2-Amino-4-(4-fluorophenyl)-5-oxo-4,5-dihydro-pyrano[3,2-*c*]chromene-3-carbonitrile (4i). White Solid, Melting point: 265-267 ºC, FT-IR (ATR)/υ (cm^{-1}): 3376, 3295, 3188, 2192, 1713, 1674, 1601; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 4.54 (s, 1H, CH), 7.17-7.21 (t, J = 8.8 Hz, 2H, Ar-H), 7.35-7.39 (td, J_1 = 3.2 Hz, J_2 = 6.8 Hz, 2H, Ar-H), 7.49-7.57 (m, 4H), 7.75-7.80 (dt, J_1 = 1.6 Hz, J_2 = 8 Hz, 1H, Ar-H),7.94-7.97 (dd, J_1 = 1.6 Hz, J_2 = 8 Hz, 1H, Ar-H).

2-Amino-4-(4-cyanophenyl)-5-oxo-4,5-dihydro-pyrano[3,2-*c*]chromene-3-carbonitrile (4j). White Solid, Melting point: 288-290 ºC, FT-IR (ATR)/υ (cm^{-1}): 3432, 3319, 3194, 2233, 2196, 1715, 1674, 1598; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 4.60 (s, 1H, CH), 7.47-7.53 (m, 6H), 7.71-7.76 (dt, J_1 = 1.6Hz , J_2 = 7.6 Hz, 1H, Ar-H), 7.78 (d, J = 8.4 Hz, 2H, Ar-H), 7.89-7.92 (dd, J_1 = 1.6 Hz, J_2 = 8 Hz, 1H, Ar-H).

2-Amino-4-(4-methoxyphenyl)-5-oxo-4,5-dihydro-pyrano[3,2-*c*]chromene-3-carbonitrile (4k). Pale yellow solid, Melting point: 241-243 ºC, FT-IR (ATR)/υ (cm^{-1}): 3401, 3322, 3217, 2194, 1707, 1664, 1596; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 3.71 (s, 3H, OCH_3), 4.41 (s, 1H), 6.75-6.73 (dd, 1H, J_1 = 8.5 Hz, J_2 = 2.5 Hz, Ar-H), 6.84-6.88 (m, 2H, Ar-H), 7.37 (s, 2H, NH_2), 7.45-7.50 (m, 2H, Ar-H), 7.72 (t, 1H, J = 7 Hz, Ar-H), 7.88-7.90 (dd, 1H, J_1 = 8 Hz, J_2 = 1.5 Hz, Ar-H). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) 55.49, 58.11, 66.34, 78.97, 101.95, 104.11, 106.59, 112.22, 113.05, 116.66, 119.34, 119.67, 124.69, 135.84, 147.93, 148.50, 152.11, 153.18, 157.92, 159.60.

2-Amino-4-(3,4-dimethoxyphenyl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (4l). White solid**,** Melting point: 228- 230 °C; FT-IR (ATR)/υ (cm^{-1}): 3377, 3313, 3188, 2195, 1699, 1666, 1604; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 3.72 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.39 (s, 1H), 6.85 (d, J = 8.5 Hz, 1H, Ar-H), 7.19 (t, J = 8 Hz, 1H, Ar-H), 7.37 (s, 2H, NH_2), 7.44-7.50 (m, 2H, Ar-H), 7.72 (t, J = 8 Hz, 1H, Ar-H), 7.90 (d, J = 8 Hz, 1H, Ar-H). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) 55.10, 58.18, 76.87, 104.28, 113.01, 113.95, 114.84, 115.32, 119.32, 124.14, 128.77, 133.31, 133.46, 135.41, 152.10, 153.09, 157.90, 158.33, 159.54, 160.42, 160.51, 164.37.

2-Amino-4-(4-hydroxyphenyl)-5-oxo-4,5-dihydro-pyrano[3,2-*c*]chromene-3-carbonitrile (4m). White Solid, Melting point: 261-263 ºC, FT-IR (ATR)/υ (cm^{-1}): 3399, 3285, 3180, 2195, 1692, 1670, 1601; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 4.33 (s, 1H), 6.70 (d, J = 8.5 Hz, 2H), 7.06 (d, J = 8.5 Hz, 2H), 7.34 (s, 2H, NH_2), 7.42-7.48 (m, 2H), 7.69 (dt, J_1 = 7.8 Hz, J_2 = 1.6 Hz, 1H), 7.89 (dd, J_1 = 7.8 Hz, J_2 = 1.4 Hz, 1H), 9.35 (s, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) 58.40, 75.11, 104.50, 113.03, 114.21, 115.12, 116.63, 119.43, 122.79, 124.68, 128.73, 133.73, 152.05, 152.97, 156.49, 157.90, 159.55, 163.91.

2-Amino-4-(4-isopropylphenyl)-5-oxo-4,5-dihydro-pyrano[3,2-*c*]chromene-3-carbonitrile (4n). Yellow solid, Melting point: 260-262 °C; FT-IR (ATR)/υ (cm^{-1}): 3387, 3297, 3199, 2201, 1710, 1668, 1634, 1604; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 1.16 (d, J = 8 Hz, 6H, $2CH_3$), 2.80-2.85 (m, 1H, CH), 4.41 (s, 1H, CH), 7.40-7.48 (m, 7H, Ar-H, NH_2), 7.67 (t, J = 8 Hz, 1H, Ar-H), 7.90 (d, J = 7.5 Hz, 1H, Ar-H). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) 23.82, 33.06, 36.56, 58.02, 103.91, 104.20, 112.96, 116.56, 119.37, 122.34, 122.53, 124.71, 126.45, 127.50, 132.99, 140.75, 147.14, 152.10, 152.33, 153.30, 158.04, 159.56.

Methyl4-(2-Amino-5-oxo-4,5-dihydropyrano[3,2-*c*] chromene-3-carbonitrile-4-yl) benzoate (4o). Yellow solid**,** Melting point: 240- 242 °C; FT-IR (ATR)/υ (cm^{-1}): 3251, 3189, 2210, 1703, 1669, 1607; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.93 (s, 3H, CH_3),4.66 (s, 1H, CH), 7.51-7.60 (m, 6H), 7.82 (td, J_1 = 1.6 Hz, J_2 = 7.6 Hz, 1H, Ar-H), 8.00 (d, J = 8.4 Hz, 3H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm)): 37.4, 43.8, 52.5, 57.7, 103.7, 113.3, 119.4, 123.0, 125.2, 128.6, 129.9, 133.5, 149.0, 152.6, 154.2,

158.4, 160.0, 164.0, 166.4.

2-Amino-5-oxo-4-(pyridin-3-yl)-4,5-dihydropyrano [3,2-*c*]chromene-3-carbonitrile (4p). Cream powder**,** Melting point: 250- 252 °C; FT-IR (ATR)/υ (cm^{-1}): 3317, 3204, 2199, 1702, 1671, 1604; ^{1}HNMR (400MHz, DMSO-d_6) δ (ppm): 4.55 (s, 1H), 7.35 (dd, J_1 = 2.8 Hz, J_2 = 4.8 Hz, 1H), 7.45 -7.49 (m, 2H), 7.52 (s, 2H), 7.69-7.77 (m, 2H), 7.90 (dd, J_1 = 1.2 Hz, J_2 = 6.8 Hz, 1H,), 8.46 (d, J = 3.6 Hz, 1H), 8.55 (d, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 35.1, 57.4, 103.4, 113.4, 117.0, 119.5, 123.0, 124.2, 125.1, 133.5, 135.8, 139.2, 148.8, 149.5, 152.7, 154.2, 158.5, 160.0.

2-Amino-5-oxo-4-pentyl-4,5-dihydropyrano[3,2-*c*] chromene-3-carbonitrile (4q).

Pale yellow solid, Melting point: 188-190 °C; FT-IR (ATR)/υ (cm^{-1}): 3323, 3196, 2202, 1701, 1665, 1606; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 0.84 (t, J = 6.8 Hz, 3H, CH), 1.25 (d, J = 3.2 Hz, 6H, CH), 1.54 -1.61 (m, 1H, CH), 1.72-1.78 (m, 1H, CH), 3.46 (t, J = 4 Hz, 1H, CH), 7.34 (s, 2H, NH_2), 7.47-7.51 (m, 2H, Ar-H), 7.73 (td, J_1 = 1.6Hz, J_2 = 7.2 Hz, 1H, Ar-H), 7.83 (dd, J_1 = 1.2 Hz, J_2 = 8 Hz, 1H, Ar-H).

RESULTS AND DISCUSSION

To optimize the reaction conditions in the synthesis of pyrano[3,2-*c*]chromene, the reaction of 4-chlorobenzaldehyde, 4-hydroxycoumarin and malononitrile was investigated, as model reaction, for various conditions (Table 2). Therefore, the best reaction condition was performed using 0.04 g of catalyst in various solvents such as H_2O, $CHCl_3$, MeOH, EtOH, DMF and H_2O/EtOH (Table 2, entries 2-7). The use of H_2O/EtOH (1:1) as solvent under reflux conditions is the most efficient condition for the model reaction with high yield and short reaction time (Table 2, entry 7). The reaction performed under solvent free conditions, gave a lower yield in comparison with those performed in the solvent (Table 2, entries 10, 11).

After determining the optimized condition, the reaction between different aldehydes with 4-hydroxycoumarin and malononitrile was considered (Table 3). In result, pyrano[3,2-*c*]chromene were synthesized in good to high yields and short reaction times.

As shown in (Table 4), performance of synthesized catalyst compared to previously reported catalysts. Nano-SiO_2/DBN can be presented as an efficacious one, among others catalyst in terms of reaction time and yields. There are many privileges in this regard simple procedure, nontoxic solvent and mild reaction conditions.

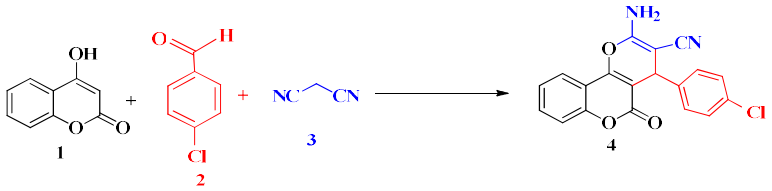
The proposed mechanism for synthesis of dihydropyrano[3,2-*c*]chromene derivatives by using nano-SiO_2/DBN is illustrated in scheme 1. Initially, the nano-SiO_2/DBN catalyst activates both the methylene group 5 and the carbonyl group 1. After, the knoevenagal condensation reaction between the malononitrile and aldehyde in the presence basic catalyst forms the intermediate 6. Then, the Michael addition of enol 4 and intermediate 6 is performed to produce the intermediate **7**. Finally, the product is formed by cyclization and tautomerization of the intermediate 8.

The reusability of the nano-SiO_2/DBN was investigated. After completion of the reaction, the nano-catalyst was separated and washed with EtOH, then dried at 70 °C. The catalyst was regained in good yields and catalyst was used in the synthesis of dihydropyrano[3,2-*c*]chromene for four times (Fig .8).

CONCLUSION

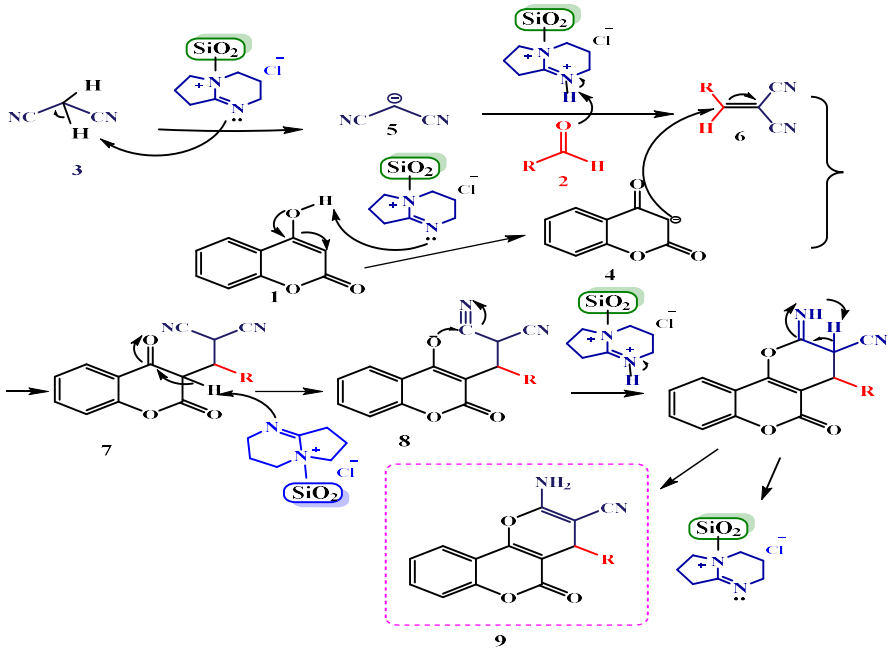
In this work, dihydropyrano[3,2-*c*]chromene derivatives were synthesized *via* one-pot, three-component condensation of aldehydes, malononitrile and 4-hydroxycoumarin in H_2O/ethanol (1:1 *v/v*) under reflux conditions. For promotion of this reaction, nano-SiO_2/DBN as heterogeneous nanocatalyst was applied under aqueous condition. The nano-SiO_2/DBN catalyst was synthesized by reaction between silica chloride and DBN. The main advantages of this procedure are high yields, short reaction times, easy work-up and reusability of catalyst.

Table 2. The Reaction of Malononitrile, 4-Chlorobenzaldehyde and 4-Hydroxycoumarin in the Presence of Nano-SiO_2/DBN under Various Conditions[a]



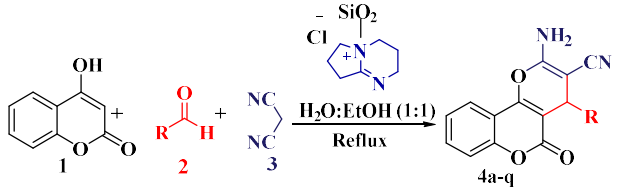
Entry	Catalyst (mol% or g)	Solvent	Conditions	Time (min)	Yield (%)[b]
1	None	EtOH/H_2O	Reflux	120	16
2	Nano-SiO_2/DBN (0.04)	EtOH	Reflux	90	70
3	Nano-SiO_2/DBN (0.04)	H_2O	Reflux	90	67
4	Nano-SiO_2/DBN (0.04)	MeOH	Reflux	90	61
5	Nano-SiO_2/DBN (0.04)	DMF	Reflux	90	58
6	Nano-SiO_2/DBN (0.04)	CH_2Cl_2	Reflux	90	23
7	Nano-SiO_2/DBN (0.04)	EtOH/H_2O	Reflux	15	95
8	Nano-SiO_2/DBN (0.04)	EtOH/H_2O	r.t	90	58
9	Nano-SiO_2/DBN (0.04)	EtOH/H_2O	100	120	54
10	Nano-SiO_2/DBN (0.04)	-	r.t	180	23
11	Nano-SiO_2/DBN (0.04)	-	100	180	42
12	Nano-SiO_2/DBN (0.01)	EtOH/H_2O	Reflux	90	52
13	Nano-SiO_2/DBN (0.02)	EtOH/H_2O	Reflux	50	65
14	Nano-SiO_2/DBN (0.03)	EtOH/H_2O	Reflux	25	70
15	Nano-SiO_2/DBN (0.05)	EtOH/H_2O	Reflux	15	95

[a]Reaction conditions: malononitrile (1 mmol), 4-chlorobenzaldehyde (1 mmol), 4-hydroxycoumarin (1 mmol). [b]Isolated yield.



Scheme 2. A proposed mechanism for synthesis of dihydropyrano[3,2-*c*]chromene derivatives by using nano-SiO_2/DBN

Table 3. Synthesis of Dihydropyrano[3,2-*c*]chromene in the Presence of Nano-SiO_2/DBN under Reflux Condition in H_2O/EtOH (1:1)[a]



Ent.	R[a]	Prod.	Time (min)	Yield (%)[b]	M.P (°C)	
					Found	Reported [ref.]
1	Ph-	4a	30	93	256-258	257-259 [48]
2	4-Cl-Ph-	4b	15	95	261-263	260-262 [48]
3	2-Cl-Ph-	4c	35	90	275-277	274-276 [48]
4	2,6-Cl_2-Ph-	4d	30	92	274-276	275-277 [49]
5	4-NO_2-Ph-	4e	20	96	261-263	256-258 [48]
6	3-NO_2-Ph-	4f	15	92	265-267	266-267 [46]
7	2-NO_2-Ph-	4g	20	92	255-257	255-256 [50]
8	4-Br-Ph-	4h	30	89	257-259	254-256 [51]
9	4-F-Ph-	4i	40	91	265-267	265-267 [46]
10	4-CN-Ph-	4j	20	93	288-290	288-290 [46]
11	4-OCH_3-Ph-	4k	30	94	241-243	237-239 [52]
12	3,4-$(OCH_3)_2$-Ph-	4l	40	90	228-230	223-235 [48]
13	4-OH-Ph-	4m	30	92	261-263	261-263 [48]
14	4-$(CH_3)_2$CH-Ph-	4n	30	90	243-245	244-245 [53]
15	4-CO_2CH_3-Ph-	4o	15	92	240-242	242-246 [46]
16	Pyridine-3-yl-	4p	40	91	250-252	248-250 [46]
17	Pentyl-	4q	25	90	188-190	188-190 [46]

[a]Reaction conditions: malononitrile (1 mmol), aldehyde (1 mmol), 4-hydroxycoumarin (1 mmol) and Nano-SiO_2/DBN (0.04 g). [b]Isolated yield.

Table 4. Comparison of Nano-SiO_2/DBN Catalyst with some other Catalyst for the Synthesis of 4b

Entry	Catalyst	Condition	Time (min)	Yield (%)[b]	(Ref.)
1	$H_6[P_2W_{18}O_{62}].18H_2O$	Reflux, H_2O/EtOH	60	87	[23]
2	SDS	Reflux, H_2O	180	88	[31]
3	Silica-supported-molybdic acid	Reflux, H_2O/EtOH	40	94	[48]
4	Si-Mg-FA	Reflux, H_2O/EtOH	60	90	[47]
5	Nano ZnO	Reflux, EtOH	90	49	[34]
6	MgO	Reflux, H_2O/EtOH	32	89	[35]
7	(S)-Proline	Reflux, H_2O/EtOH	180	72	[32]
8	P_4VPy	70 ºC, H_2O/EtOH	5	96	[43]
9	Nano-SiO_2/DBN	Reflux, H_2O/EtOH	15	95	(This work)

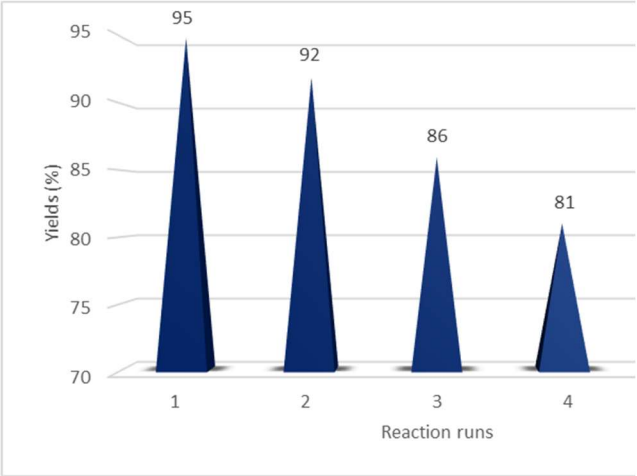


Fig. 8. Reusability of the nano-SiO_2/DBN catalyst.

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