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NiO-SnO$_2$ nano-composite efficient catalyst for the preparation of substituted pyrano[3,2-c]quinolones and pyrano[3,2-c]chromene derivatives

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ABSTRACT

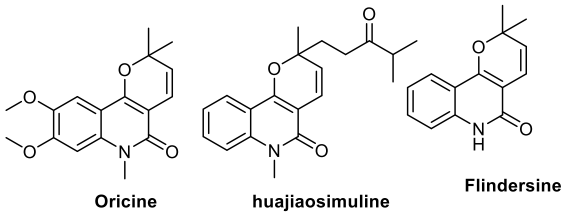
NiO – SnO$_2$ nano-composites were synthesized *via* a sol-gel method and investigated for their catalytic activity in the three-component reaction include 4-hydroxy-6-methylquinolin-2(1H)-one derivatives/4-hydroxycoumarin, aldehydes and malononitrile leading to the formation of the pyrano[3,2-c]quinolone/pyrano[3,2-c]chromene derivatives. Phase analysis of nano-composites was evaluated using XRD analysis which shows a cubic system for both magnesium aluminate and magnesium oxide phases.

Keywords: *NiO – SnO$_2$; Nickel oxide; multi-component reaction; 4-hydroxy-2H-quinoline-2-one; pyrano[3,2-c]quinolone; pyrano[3,2-c]chromene.*

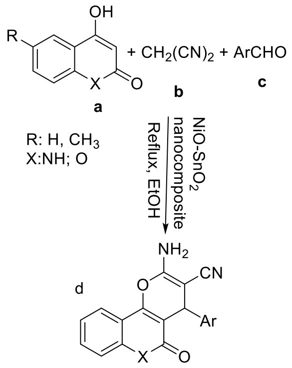
1. INTRODUCTION

Pyran and quinoline are two of the vast framework of heterocyclic compounds as they are the core of bioactive materials with interesting pharmacological effects. Also, several compounds containing quinoline welding to pyrans such as pyrano[3,2-c]quinoline also have shown valuable properties. The pyranoquinoline nucleuses have been identified in examples of natural compounds such as oricine, huajiaosimuline and flindersine bioactive drugs (Scheme 1) [1-8]. The similar structures have useful properties with a broad range of pharmacological activities such as anti-inflammatory, antibacterial, antitubercular, antiproliferative and anti-tubulin activities, selective σ1 receptor ligands, and mitotic kinesin-5 inhibitors [9-14].

Thus, the synthesis of pyranoquinolines is of great interest, because of unique properties and their functional ability as useful drugs. Among the different methods used in the preparation of pyranoquinolines, multicomponent reactions of 4-hydroxy-quinolin-2(1H)-one, malononitrile, and aldehydes is one of the simple and practical synthetic methods of these compounds. This reaction requires the use of base catalysts and published sources have reported the use of catalysts such as piperidine [15], triethanolamine [16], Tris-hydroxymethylaminomethane (THAM) [17], Na$_2$CO$_3$ [18], and di-*n*-butylamine (DBA) [19]. However, the reported strategies are effective, but, the exploration of heterogeneous catalysis which is an active strategy is in demand. In continuation of our current research [20-25], herein, we wish to report an efficient and facile procedure for the easy access of functionalized novel pyrano[3,2-c]quinolone / pyrano[3,2-c]chromenes *via* a one-pot, a three-component reaction using NiO – SnO$_2$ nanocomposite as an efficient catalyst (Scheme 2).



Scheme 1. chemical structure of oricine, huajiaosimuline and flindersine bioactive drugs.



Scheme 2. Synthesis of pyrano[3,2-c]quinolone / pyrano[3,2-c]chromenes using NiO – SnO$_2$ nano-composite as catalyst.

2. EXPERIMENTAL SECTION

Chemical materials and solvents were purchased from Merck and Aldrich chemical companies. The powder X-Ray diffraction patterns were measured with D$_8$, Advance, Bruker, axes, diffractometer using Cu-Kα irradiation. FE-SEM was taken by a Hitachi S-4160 photograph to examine the shape of the sample. A Bruker Avance DPX 400 MHz instrument was used to record NMR spectra in DMSO-d$_6$ as solvent. Elemental analysis was performed on a Heraeus CHN-O-Rapid analyzer. FE-SEM coupled with EDAX was taken by a Hitachi S-4160 photograph to examine the shape and metallic composition of the samples.

2.1. Preparation of NiO - SnO_2 nanocomposite.

2-Aminoethanol (90 mmol) was dissolved in water (50 mL) and subsequently added dropwise to a solution of Nickel chloride (20 mmol) and tin (II) chloride (20 mmol) in 100 ml of ethanol under magnetic stirring. At the end, the mixture was stirred for 1h. The resulting precipitate was filtered, washed with water several times and dried in an oven and finally calcined at 500 °C for 3h.

2.2. Typical procedure for the preparation of pyrano[3,2-c]quinolone / pyrano[3,2-c]chromenes. A mixture of **a**,**b**, **c** (each 1 mmol), and NiO-SnO_2 nanocomposite (0.025 g) was refluxed in ethanol (50%). After the completion of the reaction (TLC monitoring, EtOAc: hexane 10/90 v/v), the solid formed in the reaction mixture was dissolved in hot ethanol, filtered, and recrystallized from ethanol to afford the desired products.

2.3. Spectral data.

2-amino-9-methyl-5-oxo-4-phenyl-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carbonitrile **(Table2, product 14d)**: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.91 (s, 3H, CH_3), 4.61 (s, 1H, CH), 7.07-7.32 (m, 8H), 7.83 (d, *J* = 2.4 Hz, 1H), 10.78 (s, 1H, NH) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 21.4, 57.8, 108.2, 115.7, 116.0, 120.2, 127.4, 127.7, 128.6, 128.9, 132.2, 134.9, 139.2, 144.9, 155.3, 161.1, 163.1 ppm; Elemental Analysis for $C_{20}H_{15}N_3O_2$: found: C, 72.91; H, 4.47; N, 12.69%; calculated: C, 72.94; H, 4.59; N, 12.76%.

2-amino-4-(4-chlorophenyl)-9-methyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carbonitrile **(Table2, product 15d)**: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.91 (s, 3H, CH_3), 4.65 (s, 1H, CH), 7.08 (d, *J* = 8.0 Hz, 1H), 7.21 (s, 2H, NH_2), 7.32 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.83 (s, 1H), 11.07 (s, 1H, NH) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 21.2, 59.1, 108.9, 115.7, 116.1, 120.2, 127.8, 128.1, 128.7, 132.3, 134.7, 137.7, 139.2, 145.6, 154.6, 161.8, 163.0 ppm; Elemental Analysis for $C_{20}H_{14}ClN_3O_2$: found: C, 65.95; H, 3.82; N, 11.51%; calculated: C, 66.03; H, 3.88; N, 11.55%.

3. RESULTS SECTION

Figure 1 shows the XRD pattern, FE-SEM image, and Particle size distribution of NiO – SnO_2 nano-composite calcined at 500°C. XRD pattern states that two-phase is formed: NiO and SnO_2. NiO is crystallized in the rhombohedral phase with the characteristic peaks of 37.2, 43.3, 62.8, 75.4, and 79.4 [2θ °]. While SnO_2 with the characteristic peaks of 26.6, 33.9, 37.9, 51.8, 54.8, 57.8, 61.9, 64.8, 66.0, and 78.7 [2θ°] shows tetragonal phase.

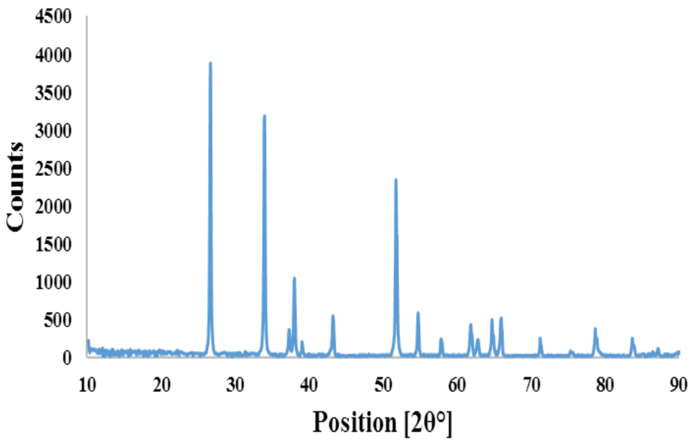


Figure 1. XRD pattern of NiO – SnO_2 nanocomposite.

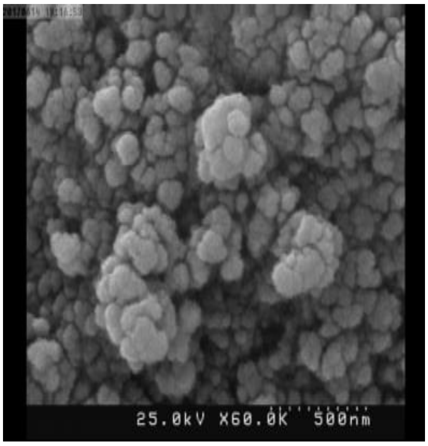


Figure 2. FE-SEM image of NiO – SnO_2 nanocomposite.

The surface morphology of nano-composite by FE-SEM indicate that the particles are relatively spherical in shape with an approximate size less than 100 nm (Figure 2). The particle size distribution curve of nano-composite performed by DLS technique is shown in Figure 3. Before analysis, the sample was dispersed in ethanol (1g in 25 mL) and sonicated for 30 min. The mean particle size of nano-composite determined by this method is approximately 72 nm.

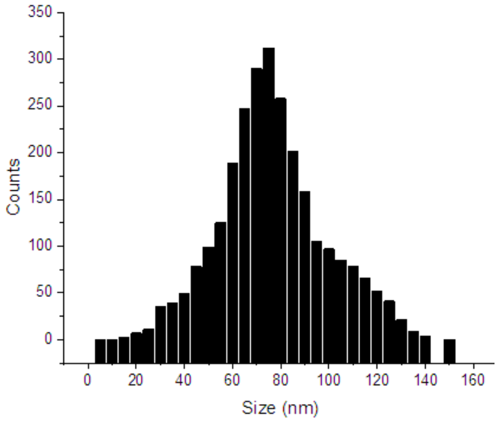


Figure 3. Particle size distribution of NiO – SnO_2 nanocomposite

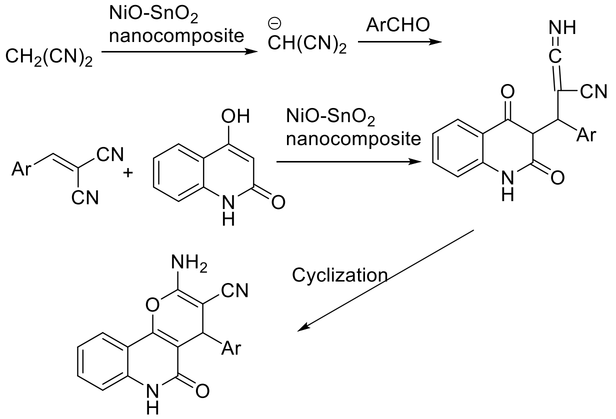
This project investigates the use of NiO – SnO_2 nanocomposite on the catalytic multi-component reaction of include 4-hydroxy-6-methylquinolin-2(1H)-one, aldehydes and malononitrile deals to the 2-amino-9-methyl-5-oxo-4-aryl-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carbonitrile derivatives.

The reaction mechanism consists of two stages. The first stage is knoevenagel condensation and the second stage gives the desired product. At first, the acidic hydrogen of malononitrile taken by the basic factors of magnesium oxide and aluminate phase and the resulting anion is reacted with an aldehyde. At this stage, with the removal of a water molecule, 2-arylidenemalononitrile intermediate is formed. This process is known as knoevenagel condensation reaction. In the next step, the desired product is obtained by the nucleophilic attack of 4-hydroxy-6-

methylquinolin-2(1H)-one to 2-arylidenemalononitrile intermediate followed by a cyclization reaction (Scheme 3).

To achieve the optimal conditions as higher yields and shorter reaction time, the condensation reaction of 4-hydroxy-6-methylquinolin-2(1H)-one (1 mmol), malononitrile (1 mmol) and benzaldehyde (1 mmol) was chosen as a model of reaction in solvent-free and in the presence of different solvents, under different temperature and catalyst dosage. The results are summarized in Table 1. According to Table 1, 0.025 g of NiO – SnO$_2$ nanocomposite as a catalyst and ethanol (50%, reflux) was selected as the optimum conditions.

Based on the optimal results obtained, various derivatives of the 2-amino-9-methyl-5-oxo-4-aryl-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carbonitrile derivatives **(1d-15d)** were prepared, and the results are summarized in Table 2. The aldehydes with electron-withdrawing or halogen groups will participate in the reaction at fewer times than those containing electron-donating groups.



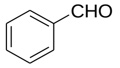
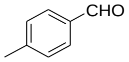
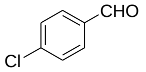
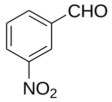
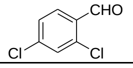
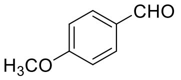
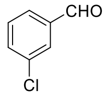
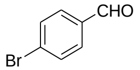
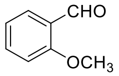
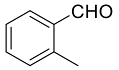
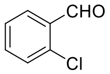
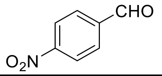
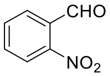
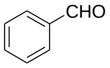
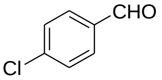
Scheme 3. Proposed mechanism for the synthesis of **1d-13d.**

Table 1. Optimization of the reaction conditions.

Entry	Cat. (g)	Solvent (3 mL)	Yield (%)^a
1	0.025	-; 100 °C	-
2	-	EtOH; Reflux	-
3	0.025	EtOH; Reflux	86
4	0.025	CH$_2$Cl$_2$; Reflux	-
5	0.025	*n*-Hexane; Reflux	-
6	0.025	EtOAc; Reflux	-
7	0.025	H$_2$O; Reflux	-
8	-	EtOH; Reflux	-
9	0.05	EtOH; Reflux	85
10	0.01	EtOH; Reflux	15
11	0.075	EtOH; Reflux	87
12	0.1	EtOH; Reflux	83

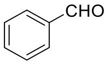
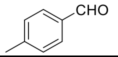
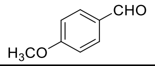
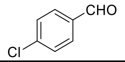
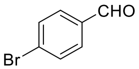
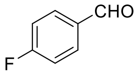
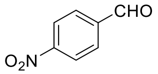
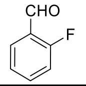
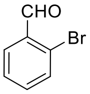
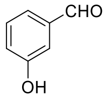
[a] Isolated Yields; based on the synthesis of 2-amino-9-methyl-5-oxo-4-phenyl-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carbonitrile, reaction time: 3h

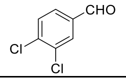
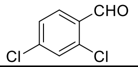
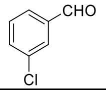
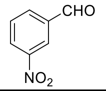
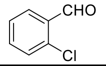
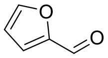
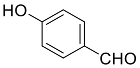
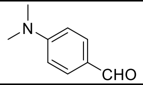
Table 2. preparation of 2-amino-9-methyl-5-oxo-4-aryl-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carbonitrile derivatives.

Entry	Aldehyde	R	Time (h)	Yield)(%)*
1d		**H**	**3**	**86**
2d		**H**	**5**	**80**
3d		**H**	**2**	**89**
4d		**H**	**2**	**91**
5d		**H**	**3**	**87**
6d		**H**	**6**	**74**
7d		**H**	**2**	**92**
8d		**H**	**2**	**90**
9d		**H**	**7**	**65**
10d		**H**	**6**	**70**
11d		**H**	**3**	**80**
12d		**H**	**2**	**83**
13d		**H**	**3**	**68**
14d		**CH$_3$**	**3**	**88**
15d		**CH$_3$**	**2**	**89**

*** Isolated Yield**

Table 3. Preparation of 2-amino-5-oxo-4-aryl-4H,5H-pyrano[3,2-c]chromene-3-carbonitrile derivatives.

Entry	Substrate	Time (h)/ Yield (%)^a
16d		**3/85**
17d		**5/79**
18d		**6/88**
19d		**2/86**
20d		**2/93**
21d		**2/96**
22d		**2/97**
23d		**3/79**
24d		**3/86**
25d		**8/90**

Entry	Substrate	Time (h)/ Yield (%)^a
26d		**2/78**
27d		**2/83**
28d		**2/84**
29d		**2/87**
30d		**3/87**
31d		**3/71**
32d		**5/69**
33d		**5/60**

^{a}Isolated yield

H-NMR spectrum of compound 15d showed nine distinct protons. The amide hydrogen (N-H) located in chemical shift (δ) of 11.07 as a single, while methyl and methanetriyl group protons appeared at chemical shift 2.91 to 4.65 respectively. The other protons are related to NH_2 and aromatic rings. In the ^{13}C-NMR spectrum of compound 3d, revealed 18 carbon signals related to C=O (163.0), methyl (21.2), methanetriyl (59.1), nitrile (108.9) groups and so-on.

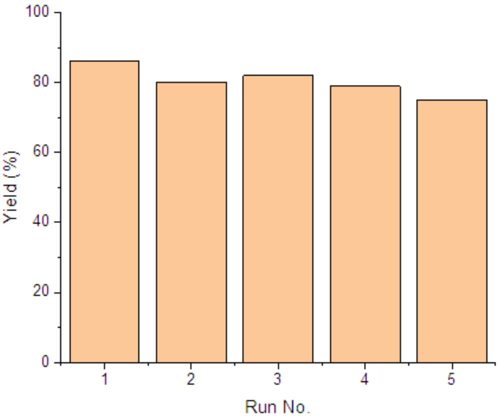


Figure 4. Reusability of NiO – SnO_2 nanocomposite.

Finally, the catalyst recovery potential was investigated. Recycled catalyst shows a high potential in the catalytic process (Figure 4).

Next, the synthesis of pyrano[3,2-c]chromene derivatives from the reaction of 4-hydroxycoumarin, aldehydes and malononitrile at optimum condition (0.025 g of catalyst, reflux in ethanol)were investigated.

Aryl aldehydes bearing electron-donating and electron-withdrawing groups successfully furnished the desired products **(16d-33d)** in good to excellent yields. However, substrates with electron withdrawing groups are more reactive than those of electron-donating groups (Table 3).

4. CONCLUSIONS

Due to the high performance and the possibility of recycling as well as the goals of green chemistry using heterogeneous catalysts in chemical reactions is growing day by day. Thus, in this study, a three-component reaction of 4-hydroxy-6-methylquinolin-2(1H)-one/4-hydroxycoumarin, aldehydes and malononitrile in mild conditions and the presence of NiO – SnO_2 nanocomposite as a heterogeneous catalyst were examined. Various derivatives of aldehydes are used, and products were synthesized in high yield. The advantages of this method is the use of a heterogeneous recoverable catalyst, and the reaction is carried out under mild conditions.

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6. ACKNOWLEDGEMENTS

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