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ORIGINAL PAPER

Convenient synthesis of spirooxindoles using SnO_2 nanoparticles as effective reusable catalyst at room temperature and study of their in vitro antimicrobial activity

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Abstract
New highly efficient method for safe, green and facile synthesis of spirooxindole derivatives have been presented. SnO_2 nanoparticles (SnO_2 NPs) as effective catalyst were synthesized through chemical precipitation method and characterized in details using FTIR, XRD, SEM and EDS methods. Obtained nano tin oxide particles were used as heterogeneous catalyst for the one-pot synthesis of spirooxindoles at room temperature. High–excellent yields of products, short reaction times, room temperature conditions and reusability of catalyst are the main advantages of this method. Evaluation of antimicrobial activity of some synthesized compounds were performed against eight bacteria. Agar diffusion method was used for determining preliminary antibacterial activities and to assess the bacterio-static activity of compounds with inhibition zone, micro-well dilution assay method was used. Obtained results showed that (**5j**) was active against all tested microorganisms and was the most effective compound.

Keywords Multicomponent reactions · Spirooxindoles · SnO_2 nanoparticles · Reusable catalyst · Antibacterial activity

Introduction

During the past decade, intensive attentions have been focused on the application of nano metal oxides as catalyst [1–6]. This is Due to reusability and high surface area of nano particles, which enhanced the collision between reactants and catalyst surfaces. In recent years, SnO_2 nano particles with unique properties, have been widely used in different fields such as anode for Lithium batteries [7], solar cells [8], gas sensors [9, 10] and catalyst in organic synthesis [3–6, 11–13].

Multicomponent reactions (MCRs) are one of the best options for the synthesis of organic compounds especially polyheterocycles [14]. MCRs provided a powerful synthetic route in which various starting materials reacted together in one pot conditions, where basically all or most of the atoms contribute to the newly formed product.

Because of spirooxindoles have interesting and unique structures with therapeutic and biological activities [15–18]. Study on the facile and applicable methods for preparation of this class of chemicals have been considered as an attractive field in organic synthesis. Recently, new pathways and various catalysts have been used for the synthesis of spirooxindoles such as cesium fluoride [19], [bmim]OH [20], *p*-TSA [21], (SB-DBU)Cl [22], $Mg(ClO_4)_2$ [23], meglumine [24], piperidine [14], carbon-SO_3H [25], bmim(OH)/chitosan/EtOH [26], chitosan/ionic liquid [27], TBA acetate [28], piperidine (under ultrasonic irradiation) [29], ($H_3N^+CH_2CH_2OH$) ($HCOO^-$) [30], NaBr [31], [BMIm]BF_4 [32], [Ch-OSO_3H]$_3W_{12}PO_{40}$ [33], gluconic acid [34] and nickel chloride [35].

Some of these methods are very sufficient and some of them performed through long reaction times and reflux conditions. Furthermore, there are few reports about the synthesis of spirooxindoles in the presence of metal oxide nanoparticles. Recently, methylene dipyridine stabilized on Fe_3O_4 nanoparticles [36], manganese ferrite nanoparticles [37] and zirconium(IV) oxide [38] have been used as catalyst for the preparation of spirooxindole derivatives. Considering

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the good efficiency of this type of catalysts, further studies on new metal oxide nanoparticles can develop new routes to the efficient synthesis of spirooxindoles. In continuation of our studies on environmentally benign multi-component synthesis of heterocyclic compounds in the presence of new catalysts [39–41], herein, we prepared, characterized and used SnO_2 nanoparticles as effective and reusable catalyst for green synthesis of spirooxindoles at room temperature. Three component reaction occurred between isatin, malononitrile (or ethyl cyanoacetate) and β-diketone (dimedone, cyclohexanedione and barbituric acid derivatives) in the presence of SnO_2 nanoparticles at room temperature and short reaction times (Scheme 1).

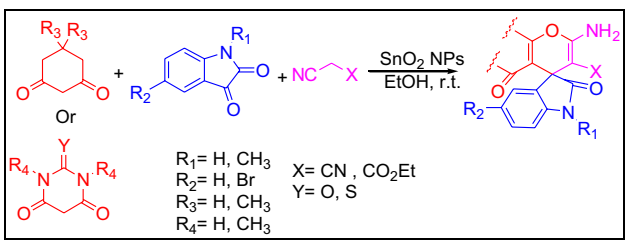
Experimental

Materials and methods

The products have separated and identified by physical and spectral data. The FTIR spectra have been recorded on FTIR Magna 550 apparatus using KBr plates. ^{1}H NMR and ^{13}CNMR spectra were recorded with a Bruker Avance DPX-400 spectrometer at 400 and 100 MHz, respectively. Powder X-ray diffraction (XRD) was carried out on a Philips diffractometer of X'pert Company with monochromatized Cu Kα radiation ($\lambda = 1.5406$ Å). Microscopic morphology of products was visualized by electron scanning microscopy (SEM) (LEO 1455VP).

Preparation of SnO_2 nanoparticles

SnO_2 nanoparticles were prepared using chemical precipitation method by dissolving 2 g (0.1 mol) of $SnCl_2$ and $2H_2O$ in 100 mL distilled water. After dissolving of tin salt, ammonia solution (25 vol%) was added dropwise to the solution through continuous stirring. The obtained gel type precipitate was filtered and dried at 80 °C for 24 h. After that, resulting powder was calcined at 550 °C for 2 h [42].



Scheme 1 Synthesis of spirooxindole derivatives catalyzed by SnO_2 nanoparticles

Typical procedure for the synthesis of spirooxindoles

A mixture of isatin (1 mmol), malononitrile (1 mmol) and dimedone (1 mmol) was stirred at room temperature in the presence of SnO_2 nanoparticles and 2 mL of EtOH. The reaction progress was monitored by TLC (*n*-hexane/ethyl acetate, 2:1 ratio). After that, the resulted mixture (containing the solid product and nano catalyst) was dissolved in acetone and filtered for separation of the catalyst. Finally, the product **5a** was obtained after evaporation of acetone and for further purification recrystallized from EtOH.

Spectral data

2-Amino-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3′-carbonitrile (5a) M.p.: 266–268 °C; FTIR (KBr): $V_{max} = 3339, 3312, 2879, 2191, 1723, 1683, 1219$ cm$^{-1;}$ ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 1.30$ (s, 6H, $2CH_3$), 1.92 (s, 2H, CH_2), 2.51 (s. 2H, CH_2), 6.79 (d, 1H, $J = 8$ Hz ArH), 6.89 (m, 2H, ArH), 6.99 (d, 1H, $J = 8$ Hz ArH), 7.25 (s, 2H, NH_2), 10.41 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 27.4, 28.1, 31.4, 47.2, 49.7, 57.8, 108.8, 111.2, 116.9, 121.1, 123.4, 128.5, 134.8, 142.3, 158.1, 163.5, 177.1, 194.4$ ppm.

2-Amino-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile (5b) M.p.: 250–252 °C; FTIR (KBr): $V_{max} = 3289, 3158, 2958, 2193, 1726, 1653, 1220, 1050$ cm$^{-1;}$ ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 1.90$ (2H, q, $J = 6.4$ Hz CH_2), 2.28 (2H, t, $J = 8$ Hz, CH_2), 2.65 (2H, t, $J = 8$ Hz, CH_2), 6.8–7.3 (4H, m, ArH), 7.24 (2H, s, NH_2), 10.41 (1H, s, NH) ppm.

2-Amino-5′-bromo-7,7-dimethyl-2′,5-dioxo-5,6,7,8 tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile (5c) M.p.: 300–302 °C; FTIR (KBr): $V_{max} = 3371, 3179, 2958, 2193, 1718, 1678, 1219, 1011$ cm$^{-1;}$ ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 1.10$ (s, 6H, $2CH_3$), 2.13 (s, 2H, CH_2), 2.52 (s, 2H, CH_2), 6.77 (s, 1H, ArH), 7.23–7.34 (m, 4H, ArH),7.36 (s, 2H, NH_2), 10.58 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 27.3, 28.1, 31.9, 39.8, 46.9, 50.1, 55.7, 110.3, 111.4, 113.2, 116.4, 126.6, 130.1, 135.8, 140.6, 157.9, 162.2, 178.1, 194.9$ ppm.

2-Amino-5′-bromo-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile (5d) M.p.: 279–281 °C; FTIR (KBr): $V_{max} = 3372, 3176, 2956, 1718, 1647, 1219, 1011$ cm$^{-1;}$ ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 1.25$–1.31 (2H, m, CH_2), 1.91 (2H, t, $J = 6.8$ Hz, CH_2), 2.26 (2H, t,

J = 6.4 Hz CH_2), 6.78 (1H, s, ArH), 7.26–7.34 (2H, m, ArH), 7.35 (2H, s, NH_2), 10.57 (1H, s, NH) ppm.

2-Amino-1′,2′,5,6,7,8-hexahydro-7,7-dimethyl-2′,5-dioxo-1′-(phenylmethyl)spiro[4H-1-benzopyran-4,3′-[3H]indole]-3-carbonitrile (5e) M.p.: 268–270 °C; FTIR (KBr): V_{max} = 3346, 2962, 2197, 1716, 1661, 1218 $cm^{-1;}$ ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.01 (6H, s, $2CH_3$), 2.10 (2H, s, CH_2), 2.42 (2H, s, CH_2), 4.91 (2H, s, CH_2), 6.46 (1H, d, J = 7 Hz, ArH), 6.98–7.39 (m, 8H, ArH), 7.43 (2H, s, NH_2) ppm.

2-Amino-1′-benzyl-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro[chromene-4,3′-indole]-3-carbonitrile (5f) M.p.: 282–284 °C; FTIR (KBr): V_{max} = 3371, 2958, 2193, 1718, 1678, 1219, 1011 $cm^{-1;}$ ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.71 (2H, m, CH_2), 1.95 (2H, t, J = 7.2 Hz, CH_2), 2.24 (2H, t, J = 8 Hz CH_2), 4.89 (2H, s, CH_2), 6.68 (1H, t, J = 7.2 Hz, ArH), 6.95–7.46 (8H, m, ArH), 7.52 (2H, s, NH_2) ppm.

2-Amino-5-oxo-7,7-dimethyl-spiro[(4H)-5,6,7,8-tetrahydrochromene-4,3′-(3′H)-1′-methylindol]-(1′H)-2′-one-3-carbonitrile (5g) M.p.: 255–257 °C; FTIR (KBr): V_{max} = 3372, 2958, 2192, 1706, 1667, 1221 $cm^{-1;}$ ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.01 (3H, s, CH_3), 1.05 (3H, s, CH_3), 2.08 (2H, s, CH_2), 2.51 (2H, s, CH_2), 3.15 (3H, s, CH_3), 6.98–7.29 (4H, m, ArH), 7.30 (2H, s, NH_2) ppm.

2-Amino-1′-methyl-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro[chromene-4,3′-indoline]-3-carbonitrile (5h) M.p.: 245–247 °C; FTIR (KBr): V_{max} = 3372, 2958, 2192, 1706, 1667, 1221 $cm^{-1;}$ ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.9–1.93 (2H, m, CH_2), 2.25 (2H, t, J = 6.8 Hz, CH_2), 2.60 (2H, t, J = 6.8 Hz, CH_2), 3.2 (3H, s, CH_3), 6.91–7.23 (4H, m, ArH), 7.29 (2H, s, NH_2) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 19.7, 26.5, 27.1, 36.5, 46.2, 58.1, 109.2, 112.1, 117.4, 122.6, 123.0, 128.5, 133.2, 143.6, 158.4, 166.1, 175.6, 195.2 ppm.

Ethyl-2-amino-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carboxylate (5i) M.p.: 258–260 °C; FTIR (KBr): V_{max} = 3371, 3245, 2956, 1718, 1670, 1219, 1011 $cm^{-1.}$ ^{1}H NMR (DMSO-d_6,400 MHz): δ = 0.90 (3H, t, J = 4.8 Hz CH_3), 1.15 (6H, s, $6CH_3$), 2.10 (2H, s, CH_2), 2.35 (2H, s, CH_2), 3.70 (2H, q, J = 6.3 Hz, CH_2), 6.64–7.12 (4H, m, ArH),7.80 (2H, s, NH_2), 10.25 (1H, s, NH) ppm.

Ethyl-2-amino-5′-bromo-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro [chromene-4,3′-indoline]-3-carboxylate (5j) M.p.: 257–259 °C; FTIR (KBr): V_{max} = 3272, 2927, 1722, 1690, 1229, 1049 $cm^{-1;}$ ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 0.92(t, J = 8.3 Hz, 3H, CH_3), 1.04 (3H, s, CH_3), 1.16 (3H, s, CH_3), 2.10 (2H, s, CH_2), 2.21 (2H, s, CH_2), 3.52 (2H, q, J = 6.1 Hz, CH_2), 6.64 (1H, m, ArH), 6.71–7.04 (3H, m, ArH), 7.80 (2H, s, NH_2), 10.25 (1H, s, NH) ppm.

7′-Amino-2,2′,4′-trioxo-1′,2′,3′,4′-tetrahydrospiro[indoline-3,5′-pyrano[2,3-d]pyrimidine]-6′-carbonitrile (6a) M.p.: 297–299 °C; FTIR (KBr): V_{max} = 3320, 3305, 2197, 1716, 1662, 1218 $cm^{-1;}$ ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 6.75 (1H, d, J = 8.4 Hz, ArH), 6.83 (1H, t, J = 7.2 Hz, ArH), 7.10 (1H, t, J = 6.8 Hz, ArH), 7.43 (1H, d, J = 11.2 Hz, ArH), 7.22 (2H, s, NH_2), 10.15 (2H, s, 2 NH), 11.08 (1H, s, NH) ppm.

7′-Amino-5-bromo-1,1′,2,2′,3′,4′-hexahydro-2,2′,4′-trioxospiro[indole-3,5′-pyrano[2,3-d]pyrimidine]-6′-carbonitrile (6b) M.p.: 221–223 °C; FTIR (KBr): V_{max} = 3320, 3305, 2197, 1716, 1662, 1218; ^{1}H NMR (DMSO-d_6, 400 MHz): σ = 66.75–7.43 (3H, m, ArH), 7.22 (2H, s, NH_2), 10.15 (1H, s, NH), 11.08 (1H, s, NH), 11.25 (1H, s, NH) ppm.

7′-Amino-5-bromo-1′,3′-dimethyl-2,2′,4′-trioxo-1′,2′,3′,4′-tetrahydrospiro[indoline-3,5′-pyrano[2,3-d]pyrimidine]-6′-carbonitrile (6c) M.p.: 295–297 °C; FTIR (KBr): V_{max} = 3376, 2197, 1731, 1684, 1662, 1194 $cm^{-1;}$ ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 3.10 (6H, s, $2CH_3$), 6.76–7.71(3H, m, ArH), 7.49 (2H, s, NH_2), 10.73 (1H, s, NH) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 28.2, 29.7, 48.1, 56.9, 86.1, 113.5, 117.2, 118.0, 126.4, 130.6, 136.3, 140.6, 151.1, 152.6, 157.9, 156.9, 178.1 ppm.

7′-Amino-1,1′,2,2′,3′,4′-hexahydro-1′,3′-dimethyl-2,2′,4′-trioxospiro[indole-3,5′-pyrano[2,3-d]pyrimidine]-6′-carbonitrile (6d) M.p.: 231–233 °C; FTIR (KBr): V_{max} = 3428, 3317, 2924, 2000, 1693, 1652, 1130 $cm^{-1;}$ ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 3.01 (6H, s, $2CH_3$), 6.71–7.51 (4H, m, ArH), 7.69 (2H, s, NH_2), 12.52 (1H, s, NH) ppm.

7′-Amino-2,4′-dioxo-2′-thioxo-1′,2′,3′,4′-tetrahydrospiro[indoline-3,5′-pyrano[2,3-d]pyrimidine]-6′-carbonitrile (6e) M.p.: 242–244 °C; FTIR (KBr): V_{max} = 3427, 2202, 1694, 1187 $cm^{-1;}$ ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 6.77–7.52 (m, 4H, ArH), 7.18 (s, 2H, NH_2), 10.39 (s, 1H, NH), 11.35 (s, 1H, NH), 12.40 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 45.1, 57.5, 85.2, 112.4, 119.6, 123.7, 124.3, 129.1, 133.7, 142.6, 163.9, 166.1, 167.9, 176.6, 183.2 ppm.

Evaluation of in vitro antimicrobial activity

Some synthesized spirooxindole derivatives (**5a, 5c, 5e, 5i, 5j**) were screened for their antibacterial activity against 8 bacterial strains. The microorganisms used in this research were provided by Iranian Research Organization for Science

and Technology (IROST). The test microorganisms were used as follows: *Escherichia coli* (ATCC 10536), *Klebsiella pneumonia* (ATCC 10031), *Shigella dysenteriae* (PTCC 1188), *Proteus vulgaris* (PTCC 1182) and *Salmonella paratyphi-A serotype* (ATCC 5702) as examples of Gram-negative bacteria, *Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (ATCC 29737) and *Staphylococcus epidermidis* (ATCC 12228) as examples of Gram-positive bacteria. Agar diffusion method was used for determining preliminary antibacterial activities and to assess the bacterio-static activity of the active compounds with inhibition zone, micro-well dilution assay method was used [43]. Tetracycline was used as positive control for bacteria and DMSO as a negative control.

Compound **5j** was active against all test microorganisms and it was the most effective compound as compared with others. This compound was most effective against *p. vulgaris* with MIC value of 250 µg/mL.

Results and discussion

In the first step of this study, SnO_2 nanoparticles were prepared by co-precipitation method [42] and the structure of SnO_2 nanoparticles was evaluated by X-ray diffraction method at room temperature. The peak position of SnO_2 nanoparticles relevant to standard pattern, demonstrated that they have been prepared at nanoscale with excellent purity (Fig. 1).

The morphology and size distribution of SnO_2 nanoparticles were estimated by SEM images. As shown in Fig. 2, the size range of nanoparticles was 20–32 nm with a good distribution. In addition, the size of nano particles calculated by Debye Scherrer equation (from XRD pattern) shows that the particle size was about 22 nm. Results from SEM and XRD, confirmed the preparation of SnO_2 particles in nano scale.

X-ray diffraction spectroscopy (EDX) as an analytical method for chemical composition evaluation of SnO_2 NPs was applied. EDX pattern of SnO_2 NPs has been displayed

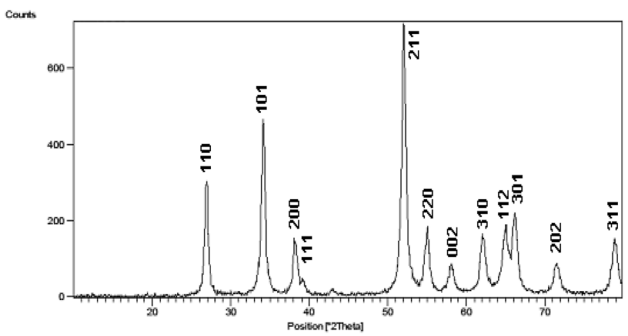


Fig. 1 XRD pattern of synthesized SnO_2 NPs

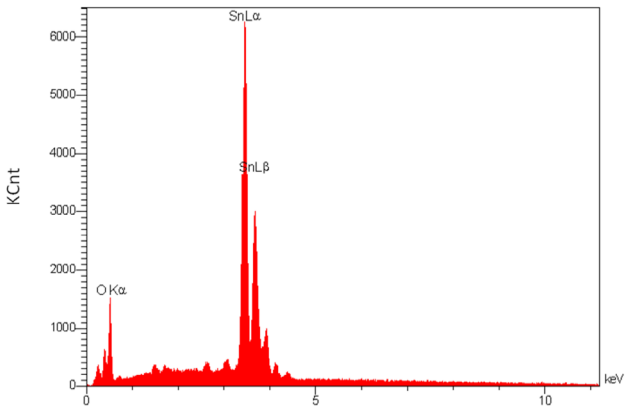


Fig. 2 SEM images of synthesized SnO_2 NPs

in Fig. 3. Strong peaks of Stannous and Oxygen was observed in this spectrum and confirmed the composition and purity of synthesized nanometal oxide.

In continue, optimum conditions of reaction including the amount of catalyst and solvent were examined. In this way, a model reaction contained isatin (1 mmol), malononitrile (1 mmol) and dimedone (1 mmol) was used in the presence of various amounts of SnO_2 NPS and different solvents. As can be seen in Table 1, when 0.01 g of catalyst was used (in EtOH), the yield of the product was 55% after 15 min (entry 3) and when 0.02 g of catalyst was applied, the yield of product become 85% after 12 min (entry 6). In continue, the effect of 0.03 g of SnO_2 nanoparticles on the yield and time of reaction was investigated. As shown in entry 9, the yield of product increased to 96% and the time of reaction decreased to 9 min. Furthermore, 0.04 g of SnO_2 nanoparticles did not improve the yield of product (entry 14). From the results in Table 1, it was clear that every amount of catalyst have the most activity when EtOH was used as solvent (entry 3, 6, 9, 14). From optimization study, it concluded that 0.03 g of SnO_2 NPs was the best amount for obtaining the highest yield in EtOH as solvent.

After determining the optimum conditions of reaction, for development of the catalyst performance, some spirooxindole derivatives were prepared using isatin derivatives, various diketones and malononitrile or ethyl cyanoacetate in the presence of SnO_2 NPs. According to results depicted in Table 2, it is clearly observed that in most cases, spirooxindole derivatives were obtained at short times and high–excellent yields. On the other hand, when ethyl cyanoacetate or barbituric acid derivatives were employed, the time of reaction was longer (**5i, 5j** and **6a**–**6f**). This is due to lower reactivity of ethyl cyanoacetate and barbituric acid derivatives versus malononitrile or dimedone derivatives [35, 44].

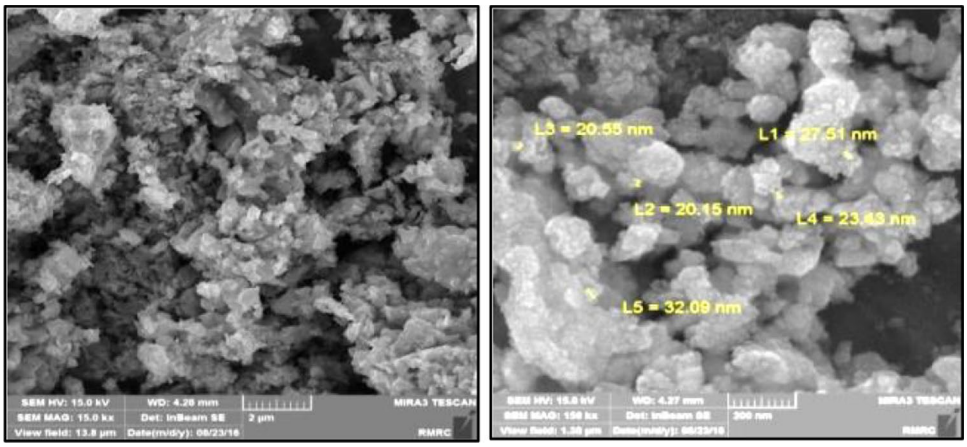
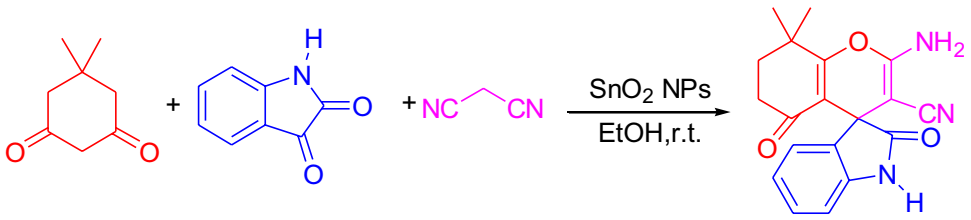


Fig. 3 EDX spectrum of SnO_2 nanoparticles

Table 1 Optimization of reaction conditions



Entry	Catalyst (g)	Solvent	Time (min)	Yield (%)[a]
1	0.01	CH_3OH	20	35
2	0.01	H_2O	30	48
3	0.01	C_2H_5OH	15	55
4	0.01	CH_3CN	120	46
5	0.01	CH_3Cl	110	35
6	0.02	C_2H_5OH	12	85
7	0.02	H_2O	20	42
8	0.02	CH_3CN	120	54
9	0.03	C_2H_5OH	9	96
10	0.03	H_2O	10	85
11	0.03	CH_3OH	8	88
12	0.03	CH_3CN	80	64
13	0.03	CH_3Cl	120	40
14	0.04	C_2H_5OH	10	90
15	0.04	H_2O	10	80

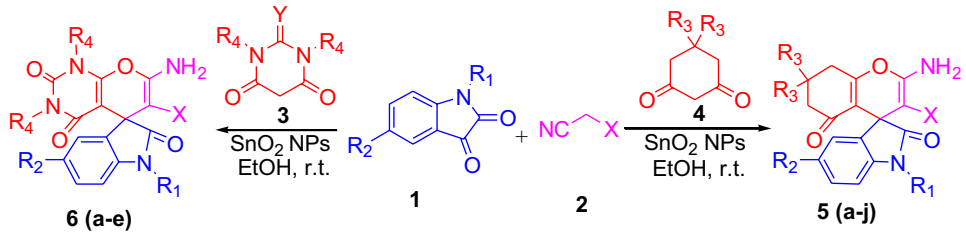
[a]Isolated yield

Reusability of catalyst

The reusability of the catalyst was examined as a measure of the efficiency of the catalyst. After the separation of product (obtained from the model reaction), the catalyst was separated and reused in the next run of the same reaction and the isolated yield of product was determined. The catalyst was reused up to five times without substantial loss of activity. The obtained yield of product from first to final run was 98–88% (Fig. 4).

A reasonable mechanism for the synthesis of mentioned products have been displayed in Scheme 2. In the first step, isatin is activated by SnO_2 nanoparticles and condensed with malononitrile (or ethyl cyanoacetate) via Knoevenagel condensation reaction to afford intermediate (I) After that, the

Table 2 Synthesis of spirooxindole derivatives using SnO_2 NPs at room temperature



3a: R_4=H, Y=O
3b: R_4= CH_3, Y=O
3c: R_4=H, Y=S

1a: R_1=H, R_2=H
1b R_1= H, R_2= Br
1c: R_1= CH_3, R_2=H
1d: R_1= CH_2Ph, R_2=H

2a: X=CN
2b: X=CO_2Et

4a: R_3=CH_3
4b: R_3=H

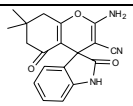
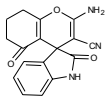
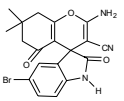
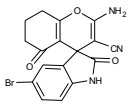
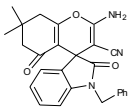
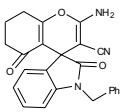
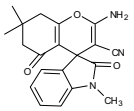
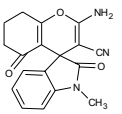
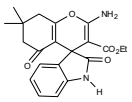
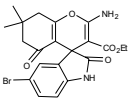
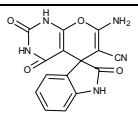
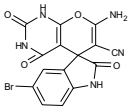
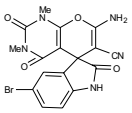
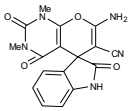
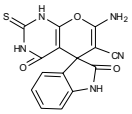
Product	Isatin	Diketon	Malonate	Product	Time (min)	Yield (%)[a]	m.p (°C)
5a	1a	4a	2a		8	96	266-268 (268-270)[45]
5b	1a	4b	2a		10	91	250-252 (251-252) [45]
5c	1b	4a	2a		20	92	300-302 (304-305) [46]
5d	1b	4b	2a		20	81	279-281 (278-280) [25]
5e	1d	4a	2a		20	95	268-270 (269-271) [47]
5f	1d	4b	2a		10	95	282-284 (283-285) [48]
5g	1c	4a	2a		8	94	255-257 (254-256) [47]
5h	1c	4b	2a		8	92	245-247 (245-246) [46]
5i	1a	4a	2b		20	82	258-260 (257-258) [45]
5j	1b	4a	2b		25	80	257-259 (260-262) [46]

Table 2 (continued)

Product	Isatin	Diketon	Malonate	Product	Time (min)	Yield (%)[a]	m.p (°C)
6a	1a	3a	2a		90	96	297-299 (296-298) [49]
6b	1b	3a	2a		110	88	221-223 (220-222) [50]
6c	1b	3b	2a		120	89	295-297 >300 [51]
6d	1a	3b	2a		100	91	231-233 (229-231) [49]
6e	1a	3c	2a		110	93	242-244 (240-241) [49]

[a] Isolated yiela

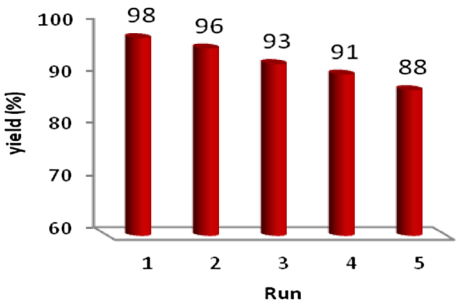
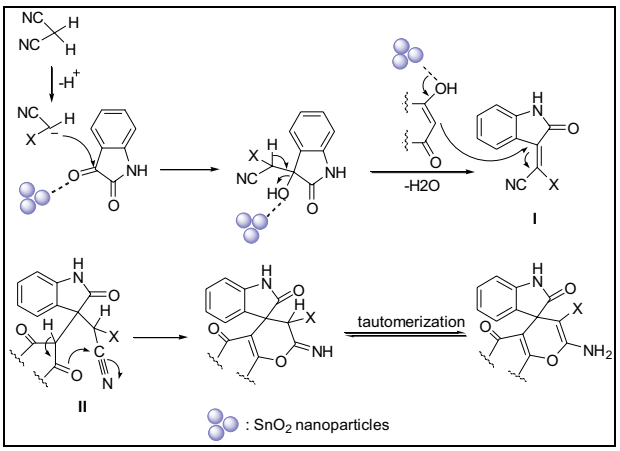


Fig. 4 Recycling behaviour of SnO_2 nanoparticles catalyst



Scheme 2 Reaction mechanism of spirooxindoles synthesis using SnO_2 NPs as catalyst

enol form of 1,3 dicarbonyl derivative attacks to intermediate I through Michael addition reaction to produce intermediate (II). Finally, cyclization and tautomerization of II lead to desired spirooxindole product.

Antibacterial activity

In this study, some synthesized compounds (**5a, 5c, 5e, 5i, 5j**) were screened in vitro for their antibacterial activities by agar diffusion method and micro-well dilution assay. The results of antibacterial activity of compounds are summarized in Table 3. As can be seen in this table, compounds **5a** and **5e** were only effective against Gram-positive bacteria, *S. epidermidis*, while compound **5i** was active against *S. epidermidis* and *S. aureus*. Also, compound **5c** showed activity against *S. epidermidis* and *E. coli*. Compound **5j** was active against all test microorganisms and it was the most effective compound as compared with others. This compound was most effective against *p. vulgaris* with MIC value of 250 µg/mL. Compound **5d** had no antibacterial activity (the results were not shown).

Finally, the efficiency of presented protocol in the synthesis of **4a** and **6a**, has been compared to some of the reported methods. As can be seen in Table 4, this method is superior in terms of reaction time, yields and temperature.

Table 3 In vitro antimicrobial activity of the synthesized compounds (**5a, 5c, 5e, 5i, 5j**)

Microorganism	**5a**		**5c**		**5e**		**5i**		**5j**		Tetracycline	
	AD	MIC	AD	MIC	AD	MIC	AD	MIC	AD	MIC	AD	MIC
S. aureus	–	–	–	–	–	–	9	2000	10	500	24	250
S. epidermidis	10	2000	10	2000	12	2000	11	2000	10	2500	39	250
E. coli	–	–	13	2000	–	–	–	–	11	2000	21	500
K. pneumonia	–	—	–	–	–	–	–	–	8	1000	22	250
S. dysenteriae	–	–	–	–	–	–	–	–	10	500	25	250
p. vulgaris	–	–	–	–	–	–	–	–	14	250	20	125
S. paratyphi-A	–	–	–	–	–	–	–	–	8	500	20	250

AD agar diffusion method, inhibition zones in diameter (mm), *MIC* minimal inhibitory concentrations as μg/mL, – no antimicrobial activity

Table 4 Study on SnO_2 NPs efficiency in compare with other reported catalysts for the synthesis of **5a** and **6a**

Entry	Catalyst	Time	*T* (°C)	Yield (%)	References
1	MgO nanoparticles	2 h	80	95	[52]
2	*N*-Benzyl-triethylammonium chloride	2 h	60	94	[48]
4	Carbon sheets with sulfonic acid	3 h	80	81	[25]
6	Functionalized mesoporous SBA-15	35 min	80	85	[53]
7	$Cu(OAc)_2,H_2O$	4 h	80	86	[54]
8	PEG-600	4 h	20	89	[55]
9	Modified β-cyclodextrin	7 h	20	91	[56]
10	SnO_2 nanoparticles	8 min	r.t.	98	This work
11	Silica@organocatalyst[a]	90 min	80	92	[57]
12	L-Prolinate supported on amberlite[a]	1 h	60	93	[58]
13	Glycerol[a]	90 min	80	91	[59]
14	*N*-Benzyl-triethylammonium chloride[a]	3 h	60	88	[48]
15	Magnesia[a]	90 min	80	88	[60]
16	1,4-Diaza-bicyclo[2,2,2]octane[a]	4 h	75	77	[61]
17	SnO_2 nanoparticles[a]	90 min	r.t.	96	This work

[a]Catalyst for the synthesis of **6a**

Conclusion

In summary, SnO_2 NPs were synthesized in a clean and soft route and showed some advantages in the preparation of spirooxindole derivatives such as short reaction times, easy work-up with high–excellent yields and low cost, as well as nontoxic catalyst. In addition, the antibacterial activity of some synthesized compounds is considerable.

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