Hydrothermal prepration of TiO_2 nanoparticles and its application in the synthesis of 3-spirochromene-2-oxindoles in water

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Abstract—**A simple and efficient one-pot three-component synthesis of the biologically important 3-spirochromene-2-oxindole scaffolds has been achieved by the reaction of isatin, active methylenes, and 1,3-dicarbonyl compounds in the presence of catalytic TiO_2 NPs in an aqueous medium. The TiO_2 nano particles catalyst has been prepared by hydrothermal method and characterized by using Raman, XRD, and HRTEM/EDAX techniques.**

Keywords-TiO_2 NPs, isatin, active methylenes, 1,3-dicarbonyl compounds, 3-spirochromene-2-oxindole

I. INTRODUCTION

TiO_2 nanoparticles (NPs) have been widely investigated particularly as a catalyst in organic synthesis. TiO_2 NPs is one of the most interesting metal oxides with respect to surface properties and thus enable organic reactions to occur. It is proved to be a good catalyst because of its high catalytic activity, non-toxicity, strong oxidizing power, reusability, and high stability [1]. Moreover TiO_2 NPs is a versatile material for industrial applications as photo catalysis for elimination of pollutant, photovoltaics, sensors, and paint industry [2]. Spiroheterocyclic skeletons are found to be sub-units in alkaloids and are used as template for drug discovery research [3]. In general, synthesis of spiro heterocyclics has been achieved either by conventional methods or based on one-pot three-component approach [4]. Due to rapid assembly of three or more reactants in one-pot, the multi-component reactions (MCRs) have become a significant synthetic tool in recent years [5]. This synthetic protocol is more prominent when the reactions are carried out in aqueous medium. The indole nucleus is the most well-known heterocyclic sub-unit present in a variety of natural products and medicinal compounds [6]. Indoles with spiro-fused heterocycles at 3-position generally show significant biological activities such as antibacterial and antifungal activities [7]. Organic synthesis in water is of current interest due to environment issues. Ever since Breslow *et al* demonstrated that hydrophobic effects of water could strongly enhance the rate of organic reactions and rediscovered the use of water as solvent in organic synthesis [8], and hence there has been a growing recognition that water is an attractive medium for organic reactions [9-13]. Several methods have been reported for the syntheses of spiro oxindoles in the presence of a number of catalysts [14-19]. However, we report a three-component reaction of isatin, malononitrile or methyl cyanoacetate and 1, 3-diketones to afford a series of spiro chromene derivatives in the presence of TiO_2 NPs catalyst prepared by hydrothermal method.

II. MATERIALS AND METHODS

A. Characterization

Melting points were determined in open capillaries and are uncorrected. Chromatography purification was conducted by column chromatography using silica gel. Solvents used for purification were of commercial grade and were purified before use. ^1H and ^{13}C NMR spectra were recorded on a Bruker spectrometer (300 MHz) or a JEOL-500MHz spectrometer (500 MHz) in DMSO-d_6 as a solvent and TMS as an internal standard. HRTEM/EDAX analyses were carried out on a HITACHI S-3400N microscope. The phase composition and crystalline nature of the catalyst was analyzed using PXRD. Bruker D8 ADVANCE MODEL diffractometer was used for recording PXRD data between 2 theta values ranging from 20 and 70 deg using CuKα as source operating at 40 kV and 30 mA. Raman spectra were recorded using a BRUKER RFS 27: Stand-alone FT-Raman Spectrometer equipped with Nd: YAG 1064 nm as excitation source.

B. Preparation of the TiO_2 NPs Catalyst

TiO_2 nanoparticles were synthesized via a hydrothermal method by using commercial TiO_2 (2.0 g) was soaked in an aqueous solution and then 20 mL of 10 M NaOH solution was added to it and pH =11 was maintained. The mixture was stirred at room temperature for two hours and then transferred to the hydrothermal reactor kept at 180 °C for 2 days. After the reaction, the mixture was cooled to RT. The resulted precipitate was washed with distilled water and further washed with 0.1 N HCl until the solution becomes neutral. After dilute HCl washing the resulted precipitate was washed with distilled water and dried in an oven (100 ºC) and calcined at 400 ºC for 24 hours. The TiO_2 NPs catalyst thus obtained was powdered and used as a catalyst.

C. Procedure for the synthesis of 3-spirochromene-2-oxindoles

A mixture of isatin **1** (1 mmol), malononitrile or ethyl cyanoacetate **2a-b** (1 mmol), 1,3 diketone **3a-b** (1 mmol) and TiO_2 NPs (50 mg) in deionized water (5 mL) was stirred at 100 °C for 10 to 30 min. (Table I). Upon completion of reaction is monitored by TLC (3:2; EtOAc: pet. ether), the reaction mixture was allowed to cool to RT. The solid was filtered off and washed with water and cold ethanol to afford desired products **4**, which was purified by flash column chromatography using EtOAc/petroleum ether.

*2-Amino-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (**4a**)*[18a]

White solid; mp 266 °C; IR ν_{max} 3378, 3311, 2963, 2193, 1722, 1655, 1220 cm^{-1}; ^1H NMR (300 MHz DMSO-d_6/TMS): δ 10.41 (s, 1H, NH), 7.24 (s, 2H, NH_2), 7.17 - 7.12 (m, 1H, ArH), 6.99 - 6.87 (m, 2H, ArH), 6.79 (d, 1H, *J* = 7.5 Hz, ArH), 2.56 - 2.51 (m, 2H, CH_2), 2.15 - 2.12 (m, 2H, CH_2), 1.03 (s, 3H, CH_3), 1.00 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6/TMS): δ 194.9, 178.0, 164.1, 158.7, 142.0, 134.4, 128.1, 122.9, 121.7, 117.3, 110.7, 109.2, 57.4, 49.9, 46.8, 31.9, 27.6, 26.9.

*2-Amino-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (**4b**)* [18a]

White solid; mp 253 ºC; IR ν_{max} 3366, 3162, 2954, 1658, 1612, 1219 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6/TMS): δ 10.45 (s, 1H, NH), 7.24 (s, 2H, NH_2), 7.21 - 6.92 (m, 3H, ArH), 6.85 (d, 1H, *J* = 7.6 Hz, ArH), 2.71 - 2.68 (m, 1H, CH_2), 2.56-2.55 (m, 1H, CH_2), 2.31 - 2.22 (m, 2H, CH_2), 1.99 - 1.97 (m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): δ 195.3, 178.3, 166.2, 158.7, 141.9, 134.5, 128.2, 123.2, 121.8, 117.4, 111.8, 109.2, 57.5, 46.9, 36.4, 26.7, 19.7.

*2-Amino-2',5-dioxo-2'H,5Hspiro[indoline-1,4'-pyrano[3,2-c]chromene]-3-carbonitrile (**4c**)* [18a]

White solid; mp 283 °C; IR ν_{max}: 3291, 2206, 1716, 1671, 1607, 1469, 1360, 1107 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6/TMS) δ 10.69 (s, 1H, NH), 7.95 (d, 1H, J = 7.8 Hz, ArH), 7.80 - 7.74 (m, 1H, ArH), 7.69 (s, 2H, NH_2), 7.57 -7.48 (m, 2H, ArH), 7.25 - 7.20 (m, 2H , ArH), 6.94 (t, 1H, J = 7.5 Hz, ArH), 6.88 – 6.78 (m, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6/TMS) δ 177.1, 158.4, 158.2, 155.1, 152.0, 142.2, 133.6, 133.0, 128.9, 124.9, 124.1, 122.7, 122.0, 116.9, 116.6, 112.4, 109.5, 101.4, 57.0, 47.6 .

*4,3'-Spiro[(6-amino-5-cyano-3-methyl-2H,4H-pyrano[2,3-c] pyrazolo)-2'-oxindole] (**4d**)* [19b]

White solid; mp >300 °C; IR ν_{max}: 3755, 3339, 3136, 2182, 1711, 1641, 1584, 1499 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6/TMS) δ 12.31 (s, 1H, NH), 10.62 (s, 1H, NH), 7.27 - 7.23 (m, 3H, ArH), 7.02 (s, 2H, NH_2), 6.92 (d, 1H, J = 7.5 H z , ArH), 1.54 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6/TMS) δ 178.0, 162.4, 155.2, 141.5, 134.7, 132.6, 128.9, 124.5, 122.5, 118.7, 109.7, 95.4, 55.1, 47.3, 8.9.

*Ethyl 2-amino-3-cyano-6-methyl-2'-oxo-spiro[indoline 3',4-pyran]-5-carboxylate (**4e**)* [18b]

White solid; mp 259 °C; IR ν_{max}: 3468, 2187, 1659, 1624, 1475, 1379, 1212 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6/TMS) δ 10.46 (s, 1H, NH), 7.24 - 7.21 (m, 3H, NH_2, ArH), 7.11 (d, 1H, J = 7.2 Hz, ArH), 7.02 - 6.99 (m, 1H , ArH), 6.85 (d, 1H, J = 7.5 Hz, ArH), 3.85 - 3.80 (m, 2H, CH_2,), 2.37 (s, 3H, CH_3), 0.84 (t, 3H, J = 7.1 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6/TMS) δ 178.5, 164.5, 158.9, 158.5, 142.1, 134.5, 128.5, 123.3, 121.8, 117.4, 109.3, 104.6, 60.2, 56.5, 48.9, 18.5,12.9.

*2-Amino-1'-methyl-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (**4f**)* [18a]

White solid; mp 253 °C; IR ν_{max}: 3365, 2196, 1657, 1613, 1465, 1354, 1218 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6/TMS) δ 7.30 - 7.25 (m, 1H, ArH), 7.23 (s, 2H, NH_2), 7.06 - 6.98 (m, 3H, ArH), 3.13 (s, 3H, CH_3), 2.57 - 2.50 (m, 2H, CH_2), 2.11 (d, 2H, J = 7.5 Hz, CH_2), 1.03 (s, 3H, CH_3), 0.99 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6/TMS) δ 200.4, 182.0, 169.7, 164.4, 149.1, 139.0, 133.9, 128.3, 127.9, 122.7, 116.2, 113.7, 62.5, 55.4, 51.9, 37.5, 33.0, 32.6, 31.9.

*2-Amino- 1'-methyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (**4g**)* [18a]

White solid; mp 245 °C; IR ν_{max}: 3466, 2195, 1651, 1609, 1471, 1354, 1217 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6/TMS) δ 7.29 - 7.25 (m, 1H, ArH), 7.08 (s, 2H, NH_2), 7.07 – 6.98 (m, 3H, ArH), 3.14 (s, 3H, CH_3),

2.67 (br, s, 2H, CH_2), 2.20 (br, s, 2H, CH_2), 1.92 (br, s, 2H, CH_2); ^{13}C NMR (75 MHz, DMSO-d_6/TMS) δ 194.9, 176.6, 166.1, 158.7, 143.5, 133.6, 128.3, 122.9, 122.4, 117.2, 111.8, 108.1, 57.1, 46.5, 36.3, 26.7, 26.3, 19.7.

*2-Amino-1'-methyl-2',5-dioxo-2'H,5H-spiro[indoline-1,4'-pyrano[3,2-c]chromene]-3-carbonitrile (**4h**)* [19a]

White solid; mp 282 °C; IR ν_{max}: 3594, 2208, 1679, 1607, 1466, 1362, 1177 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6/TMS) δ 8.01 (d, 1H, J = 8.1 Hz, ArH), 7.73 - 7.68 (m, 2H, ArH), 7.55 (s, 2H, NH_2), 7.49 - 7.31 (m, 2H, ArH), 7.16 (d, 1H, J = 7.2 Hz, ArH), 7.07 - 6.99 (m, 2H, ArH), 3.27 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6/TMS) δ 175.6, 158.6, 158.2, 155.1, 152.0, 143.5, 133.2, 132.0, 128.9, 124.6, 123.3, 122.9, 122.7, 116.7, 116.3, 112.4, 108.2, 101.2, 57.2, 47.2, 26.4.

III. RESULT AND DISCUSSIONS

The TiO_2 NPs synthesised by hydrothermal method has been characterised as follows: HRTEM images (Fig. 1a) of the TiO_2 materials viewed along the (1 0 0), (0 0 2), (1 0 1), (1 0 2), (1 1 0), and (1 1 0) directions showed well-ordered hexagonal Wurtzite TiO_2 arrays of C_{6V} symmetry, indicating that a two-dimensional (2D) ordered hexagonal structure can be well retained after the high-temperature sintering treatment, which was further demonstrated by the low-angle XRD patterns (Fig. 1c). The average pore size and wall thickness is found to be about 5 and 10 μm, respectively. HRTEM images (Fig. 1a) clearly showed the highly crystalline nature TiO_2 nanoparticles. A well-defined crystalline lattice can be identified with a d-spacing of 300 nm corresponding to the (1 0 1) plane of TiO_2 (Fig 1a). TiO_2 nanostructure linked was obtained from this simple wet-hydrothermal synthesis. These cubes are found as 5–10 μm long and 300–500 nm in diameters. Synthesized TiO_2 NPs sample was also examined by XRD and the data of the product; it describes the crystalline nature of the TiO_2 NPs with peaks corresponding to (1 0 0), (0 0 2), (1 0 1), (1 0 2), (1 1 0), (1 0 3), (2 0 0), (1 1 2), (2 0 1), (0 0 4) and (2 0 2) planes of hexagonal Wurtzite TiO_2. All the peaks could be indexed to hexagonal TiO_2 with lattice constants a = 3.285, c = 5.126. The spacing values and relative intensities of the peaks coincide with the JCPDS card no. 36-1451 for TiO_2 .The strong and narrow diffraction peaks of the XRD pattern indicate that the product has good crystalline nature (Fig. 1c). Raman spectroscopy was used to provide additional information on the properties of the synthesized TiO_2 nanoparticles. Fig. 1d shows Raman spectra consisting of several bands correspond to Raman-active phonon modes of hexagonal wurtzite TiO_2 nanoparticles with C_{6V} symmetry. The dominant line at 441 cm^{-1} corresponds to the E_2 (high) vibration mode is a characteristic band of wurtzite phase with orientation in the c-axis. The spectrum also showed a forbidden mode at 272 cm^{-1} frequency of second order described by E_2 (high) E_1 (low) phonons. The peak at 637 cm^{-1} corresponds to the A_1 (LO) and E_1 (LO) vibration modes which indicate the crystal disorder if the peaks are shifted to a different frequency. The peak at 637 cm^{-1} is a combination of the two modes, thus very broad and enhanced by disorder though they remain at lower intensity due to more ordered wurtzite structures as seen in the peak at 441 cm^{-1}. The E_1 (LO) also indicates oxygen deficiencies, which is consistent with EDS data. The peaks at 146 and 637 cm^{-1} correspond to E_g. These peaks are usually present due to the structural or doping induced disorder in the TiO_2 substrates.

The catalytic behavior of the TiO_2 NPs catalyst was studied for the synthesis of 3-spirochromene-2-oxindoles (2-amino-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro [chromene- 4,3'-indoline]-3-carbonitrile **4a**). Thus, a reaction of isatin **1a**, malononitrile **2a** and 5,5-dimethyl-1,3-cyclohexanedione **3a** in the presence of TiO_2 NPs as catalyst with a number of solvents and varied conditions have been explored (Scheme 1). Among the various optimization parameters for the reaction analyzed (Table 1), it was found to be that water was a solvent of choice and the desired product was obtained in excellent yield (Table 1, Entry 6).

Encouraged by the preliminary result and in order to demonstrate the method as general, under the optimized condition, reactions of isatin with a number of cyanoacetic acid derivatives **2a,b** and 1,3-dicarbonyl compounds **3a,b** have been investigated. All the reaction proceeded well to afford respective 3-spirochromene-2-oxindoles **4a-i** (Table 2) in high yields. The results are summarized in Table 2. The results are significant in terms of yields and product purity in all the cases when TiO_2 NPs was used as catalyst, whereas without TiO_2 NPs, the reactions needed long period of time (40 min) to complete and the yield of products were also found to be low (< 60%).

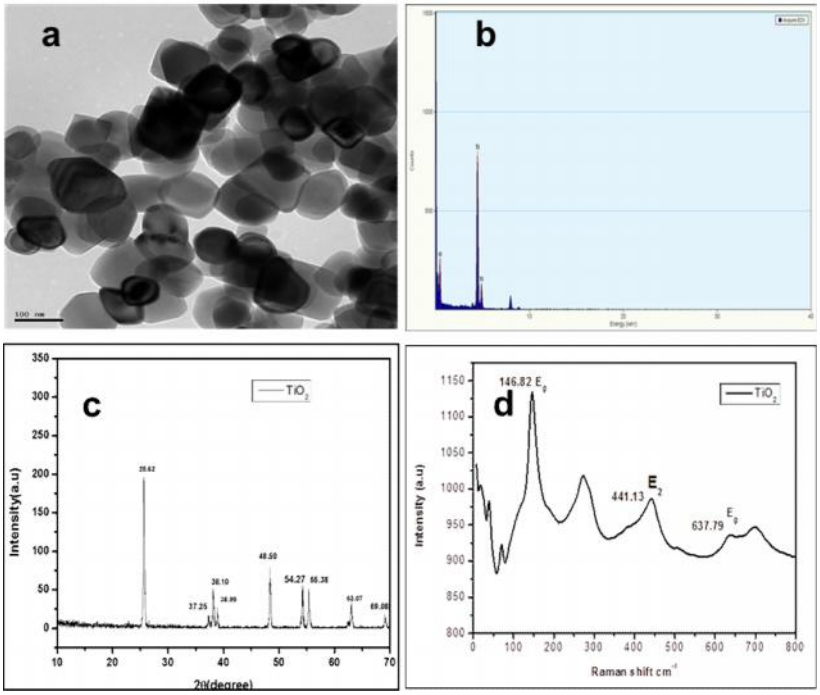
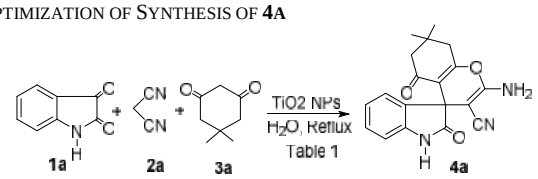


Figure 1. (a) HRTEM (b) EDX (c) XRD and (d) Raman of TiO_2 NPs

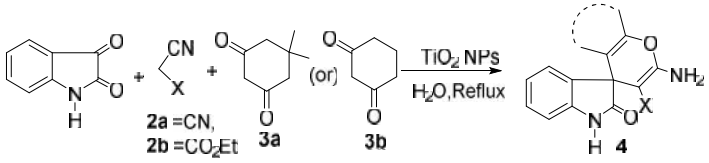
TABLE I. OPTIMIZATION OF OPTIMIZATION OF SYNTHESIS OF **4A**



Entry	Solvent	TiO_2 (mg)	Temp (°C)	Time (min)	Yield (%)
1	MeOH	50	Reflux	25	34
2	EtOH	50	Reflux	30	37
3	CH_3CN	50	Reflux	30	40
4	H_2O	50	r. t	90	30
5	H_2O	50	60	60	50
6	H_2O	50	Reflux	10	95
7	H_2O	20	Reflux	20	85

In conclusion, Preparation and characterization of TiO_2 NPs by hydrothermal method has been achieved. The catalytic application of the catalyst thus synthesized has been demonstrated for a simple, one-pot, three-component reaction for the synthesis of spiro chromene derivatives in water.

TABLE II SYNTHESIS OF SPIRO CHROMENE DERIVATIVES OF ISATIN



Entry	Substrate			Time (min.)	Product	Yield %	Mp (°C)
	R_1	X	Ketone				
1	**1a**	**2a**	**3a**	10	**4a**	95	266
2	**1a**	**2a**	**3b**	15	**4b**	90	253
3	**1b**	**2a**	**3a**	25	**4c**	57	253
4	**1b**	**2a**	**3b**	25	**4d**	52	245
5	**1b**	**2b**	**3a**	30	**4e**	21	247
6	**1b**	**2b**	**3b**	30	**4f**	62	242
7	**1c**	**2a**	**3a**	30	**4g**	73	265
8	**1c**	**2a**	**3b**	30	**4h**	77	252
9	**1d**	**2a**	**3a**	15	**4i**	95	252

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