

Synthesis of new pyridine derivatives using Ag/TiO₂/Fe₃O₄@MWCNTs MNCs as efficient organometallic nanocatalyst

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Received: December 2020; Revised: January 2021; Accepted: January 2021

Abstract: In this study a new and procedure was reported for the synthesis of Ag/TiO₂/Fe₃O₄@MWCNTs MNCs as a new heterogeneous organometallic catalyst. XRD, FESEM, EDX and TEM analysis were used for confirming the structure of synthesized nanocatalyst. The Ag/TiO₂/Fe₃O₄@MWCNTs MNCs as a high performance catalyst was employed for the preparation of a new family of functionalized spiro pyridine via the one-pot condensation reactions of enamine, isatin, malononitrile and electron deficient acetylenic compounds in water at room temperature.

Keywords: Spiropyridine, Antioxidant activity, Antimicrobial activity.

Introduction

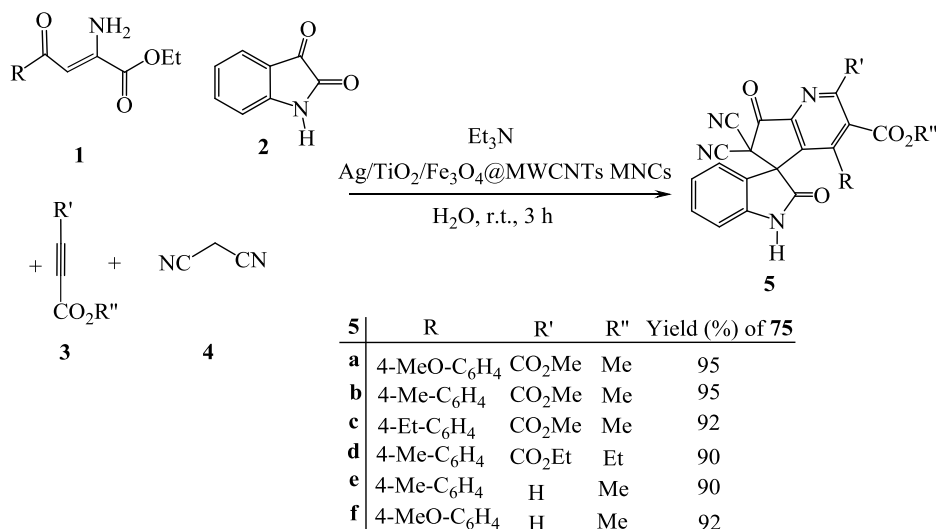
Among the heterocyclic compounds, pyridine and their analogues are the most interesting structural units due to their broad spectrum of applications [1] in natural products [2] pharmaceutical [3] agrochemical [4] and material science [5, 6]. Many of the fused pyridine compounds have been confirmed as valuable candidates possessing anti-bacterial [7], anti-fungal [8], anti-microbial [9], anti-oxidant [10, 11], anti-cancer [12, 13], anti-psychotic [14], anti-inflammatory [15, 16], anti-leishmanial [17], anti-viral [18], antihypersensitive [19], anti-convulsants [20], anti-malarial [21], potassium channel openers [22], anti-diabetic [23] and anti-tumor activities [24]. Spiro compounds having cyclic structures fused at a central carbon are of interest due to their interesting conformational features and their structural implications on biological systems [25].

The asymmetric characteristic of the molecule due to the chiral spiro carbon is one of the important criteria of the biological activities. The presence of the sterically constrained spiro structure in various natural products also adds to the interest in the investigations of spiro compounds.[26] TiO₂ because of having appropriate band gap, strong oxidizing ability, long-term stability against photocorrosion and chemical corrosion, low cost and facile preparation. [27-31] is one of the most promising materials for solar energy conversion. Transition metal oxides nanostructures due to their unique features such as high specific surface area, chemical stability and electrochemical activity at nanoscale with promising applications in applied science and technology [32] have been broadly utilized. MWCNTs due to having many convenient properties such as large surface area and high adsorption capacity [33] have been widely investigated. TiO₂ has attracted increasing attention due to excellent chemical stability, nontoxicity and low cost [34-38] The coupling of CNTs and TiO₂-NPs

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has been proved to enhance its performance [39]. The size of TiO₂ is so small that it is difficult to be separated from reaction media, which easily causes secondary pollution.[40-41] Magnetic separation is a quicker and more effective technique than traditional separation technology including centrifugation and filtration which helps to separation of nano-sized materials [42-44]. To date, Fe₃O₄ magnetic nanoparticles (MNPs) due to their high surface reactivity and facile recovery and recycling have attracted considerable interest. In this work, the our purpose is finding out new procedures for synthesis of

significant organic compounds [45-55], we investigated a procedure for the preparation of some spiropyridine derivatives **7** via the multicomponent reactions of acetophenones **1**, diethyloxalate **2**, ammonium acetate **3**, isatin **4**, malononitrile **5** and electron deficient acetylenic **6** compounds in the presence of catalytic amount of Ag/TiO₂/Fe₃O₄@MWCNTs MNCs and Et₃N in water at room temperature with excellent yields (Scheme 1).



Scheme 1: Synthesis of functionalized spiropyridines

Result and Discussion

In this research, the new spiropyridine derivatives **7** have been generated in high yields using six component reactions of methyl ketones **1**, diethyloxalate **2**, ammonium acetate **3**, isatin **4**, malononitrile **5** and electron deficient acetylenic compounds **6** in the presence of catalytic amount of Ag/TiO₂/Fe₃O₄@MWCNTs MNCs and Et₃N in water at room temperature (Scheme 1).

For confirmation the structure of novel Ag/TiO₂/Fe₃O₄@MWCNTs MNCs, we utilized SEM, XRD, EDX, VSM and TEM analysis. For determination and confirmation the construction of novel Ag/TiO₂/Fe₃O₄@MWCNTs MNCs, we employed the scanning electron microscopy images

(SEM) (Figure 1). Figure 2 shows the SEM images of Ag/TiO₂/Fe₃O₄@MWCNTs MNCs microspheres. The XRD analysis of Ag/TiO₂/Fe₃O₄@MWCNTs MNCs is exhibited in the Figure 3 for confirmation the particle size (Figure 2).

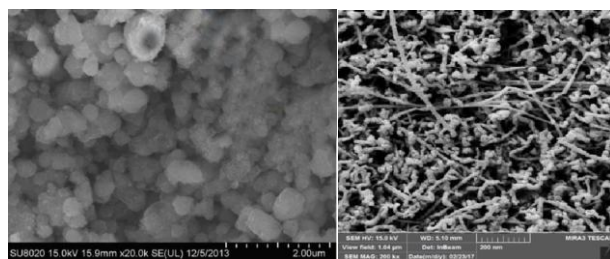


Figure 1: The SEM image of (a) Ag/TiO₂/Fe₃O₄ MNCs and (b) Ag/TiO₂/Fe₃O₄@MWCNTs MNCs

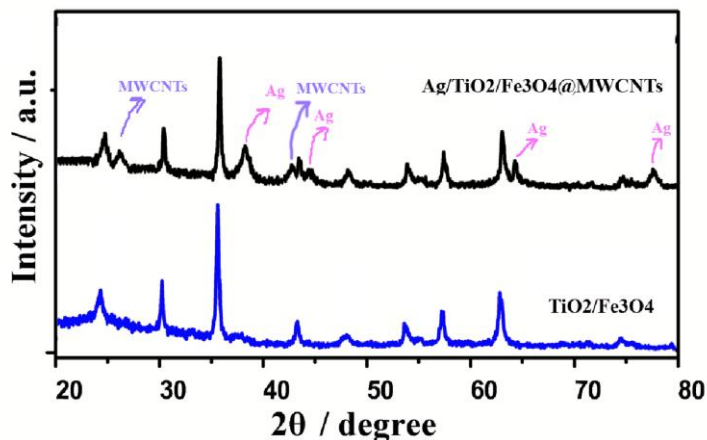


Figure 2: X-ray diffraction spectra of Ag/TiO₂/Fe₃O₄@MWCNTs MNCs.

RD measurements were carried out to investigate the crystal identity of Ag/TiO₂/Fe₃O₄ MNCs and Ag/TiO₂/Fe₃O₄@MWCNTs MNCs (Figure 2). The diffraction peaks at $2\theta = 25.2^\circ$, 38.0° , 48.2° , 54.2° , 55.1° , 63.0° , 69.0° and 75.3° are determined the presence of TiO₂ nanoparticles in the anatase phase (JCPDS, No. 21-1272). The diffraction peaks at $2\theta = 35.0^\circ$, 44.0° , 54.2° , 57.2° and 63.0° indicate the presence of Fe₃O₄ MNPs (JCPDS No. 19-629). The peaks at $2\theta=38.3$ and 46.2° correspond to (1 1 1) and (2 0 0) planes of face-centered cubic (fcc) lattice of metallic Ag (JCPDS file no. 04-0783) which can indicate that the Ag NPs do exist in the composites. A broad crystalline peak of MWNTs around 26.0° and 43.5° was observed, which represents the characteristic peak of MWNTs (JCPDS No. 41-1487).

The average crystallite size (D) of catalyst is estimated using Scherrer's equation:

$$D = k\lambda/\beta \cos \theta$$

Where crystallite size (nm) and crystallite shape factor (0.90) was shown by D and k respectively. X-ray wavelength for CuK α (0.15418 nm), the full-width-half-maximum (FWHM) of the peak and Bragg angle was shown by λ , β and θ respectively. The crystallite size was achieved 25 nm according to Scherrer's equation for the peak at 35.0° .

To further examine the morphology of the Ag/TiO₂/Fe₃O₄@MWCNTs MNCs, the samples were considered by TEM, as displayed in Figure 3. It can be seen that Ag/TiO₂/Fe₃O₄MNCs are supported on the MWCNTs.

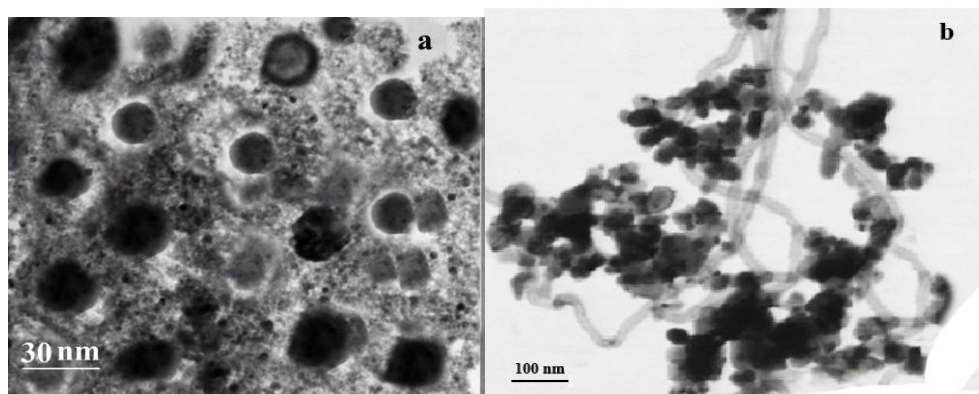


Figure 3: TEM image of the a) Ag/TiO₂/Fe₃O₄ MNCs b) Ag/TiO₂/Fe₃O₄@MWCNTs MNCs

The elemental composition of Ag/TiO₂/Fe₃O₄@MWCNTs MNCs was investigated by the Energy dispersive X-ray spectroscopy (EDS) spectrum. It was confirmed that

Ag/TiO₂/Fe₃O₄@MWCNTs MNCs were consisted of C, Ti, Ag, Fe and oxygen (Figure 4).

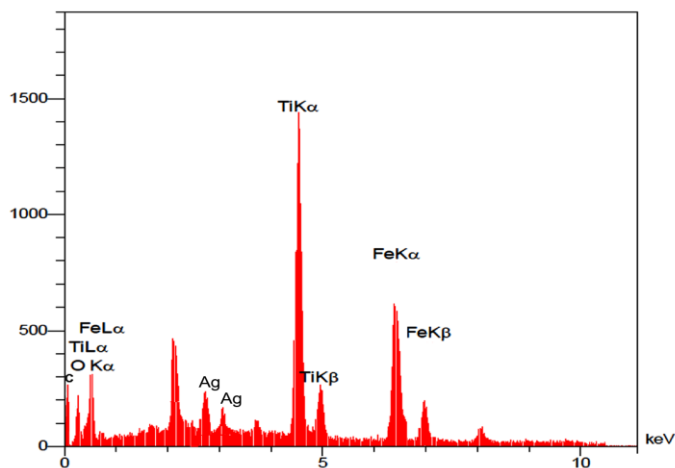


Figure 4; The EDS image of Ag/TiO₂/Fe₃O₄@MWCNTs MNCs

Figure 5 shows the saturation magnetization (*M_s*) values of the magnetic Ag/TiO₂/Fe₃O₄@MWCNTs MNCs and pure Fe₃O₄ NPs. Both of two catalysts displayed superparamagnetic property with a negligible of coercivity and remanence. As exhibited in Figure 5 the *M_s* of the Ag/TiO₂/Fe₃O₄@MWCNTs MNCs (24.3 emu/g) was weakened to a large extent

compared to that of pure Fe₃O₄ MNPs (67.5 emu/g). The magnetic Ag, Fe₃O₄ MNPs and TiO₂ NPs on carbon nanotubes can cause to the decreasing of the magnetic property. However, this value is high enough for the separation of nanocomposite by an external magnet from the aqueous solution.

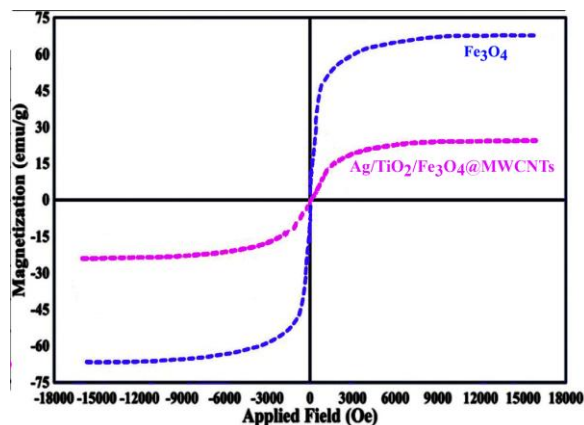


Figure 5: VSM analysis of the Ag/Fe₃O₄/TiO₂@MWNTs MNCs

Catalytic properties of Ag/TiO₂/Fe₃O₄@MWCNTs MNCs:

We also evaluated the catalytic activities of the Ag/TiO₂/Fe₃O₄@MWCNTs MNCs through the synthesis of spiropyridine derivatives in the presence Ag/TiO₂/Fe₃O₄@MWCNTs MNCs. The important section in this research is optimization of reaction condition. For this reason, initially, the reaction of 4-methoxyacetophenone **1a**, diethylxalate **2**, ammonium acetate **3**, isatin **4**, malononitrile **5** and dimethyl acetylenedicarboxylate **6a** was utilized as a sample reaction (Table 1). This reaction have low yield without catalyst even after 8 h in the presence of Et₃N (10 mol%) (entry 1, 2, Table 1). For this reason, ZnO NRs (10 mol%) was added as sample catalyst to the mixture of reaction. The yield of **7a** was achieved 45%

after 5 h (entry 3 Table 1). Another catalyst such as pyridine, K₂CO₃, Ag/TiO₂ NPs, ZnO NRs, Pyridine, Ag/Fe₃O₄ MNPs and Ag/TiO₂/Fe₃O₄ MNCs, are evaluated in the sample reaction for more investigation the effect of catalyst. As a result, these outcomes exhibited the Ag/TiO₂/Fe₃O₄@MWCNTs MNCs are the best catalyst for this reaction.

Table 1. Investigation of solvent, catalyst and temperature effect on the condensation reaction of compound **5a**

| Entry | Catalyst | Catalyst amount (mol%) | Solvent ^a | Temp. ^b | Time ^c | Yield (%) ^d |
|-----------|---|------------------------|-----------------------|--------------------|-------------------|------------------------|
| 1 | - | - | - | r.t. | 12 | trace |
| 2 | - | - | EtOH | 100 | 12 | trace |
| 3 | Et ₃ N | 10 | EtOH | r.t. | 5 | 15 |
| 4 | Et ₃ N | 15 | EtOH | r.t. | 4 | 15 |
| 5 | Et ₃ N | 20 | EtOH | 100 | 4 | 20 |
| 6 | Et ₃ N | 20 | H ₂ O | r.t. | 3 | 20 |
| 7 | Et ₃ N | 20 | CH ₃ CN | r.t. | 3 | 25 |
| 8 | Pyridine | 10 | H ₂ O | r.t. | 3 | 15 |
| 9 | Pyridine | 10 | CH ₃ CN | r.t. | 3 | 20 |
| 10 | K ₂ CO ₃ | 10 | H ₂ O | r.t. | 6 | 30 |
| 11 | K ₂ CO ₃ | 10 | CH ₃ CN | r.t. | 5 | 30 |
| 12 | K ₂ CO ₃ | 10 | EtOH | r.t. | 5 | 25 |
| 13 | Ag/TiO ₂ NPs | 10 | H ₂ O | r.t. | 4 | 65 |
| 14 | Ag/Fe ₃ O ₄ MNPs | 10 | CH ₃ CN | r.t. | 4 | 70 |
| 15 | Ag/TiO ₂ NPs | 10 | EtOH | r.t. | 4 | 60 |
| 16 | Ag/TiO ₂ /Fe ₃ O ₄ | 10 | H ₂ O | r.t. | 4 | 75 |
| 17 | Ag/TiO₂/Fe₃O₄@MWCNTs MNCs | 10 | H₂O | r.t. | 3 | 95 |
| 18 | Ag/TiO ₂ /Fe ₃ O ₄ @MWCNTs MNCs | 10 | CH ₃ CN | r.t. | 3 | 90 |
| 19 | Ag/TiO ₂ /Fe ₃ O ₄ @MWCNTs MNCs | 15 | CH ₃ CN | r.t. | 3 | 93 |

| | | | | | | |
|----|--|----|--------------------|------|---|----|
| 20 | Ag/TiO ₂ /Fe ₃ O ₄ @MWCNTs MNCs | 10 | EtOH | r.t. | 3 | 85 |
| 21 | ZnO (NRs) | 10 | H ₂ O | r.t. | 3 | 65 |
| 22 | ZnO (NRs) | 10 | CH ₃ CN | r.t. | 3 | 65 |

^aThe amount of solvent was 5 mL.

^bTemperature (°C) for reaction conditions

^cTime (h) for reaction conditions

^dIsolated yield

When Ag/TiO₂ NPs and Ag/Fe₃O₄ MNPs were used as a separate catalyst, the yields were lower than Ag/TiO₂/Fe₃O₄@MWCNTs MNCs (Table 1, entry 13 and 14). As shown in outcomes, different amounts of catalyst Ag/TiO₂/Fe₃O₄@MWCNTs MNCs (10-20 mol%) were utilized for the discovering the best amounts of catalyst. The results of investigation displayed that 10 mol% is the best amounts of catalyst for this reaction. By increasing the amount of catalyst from 10 mol%, didn't seen any significant variation in the yields of reaction (entry 18, 19, Table 1). Also, by raising the reaction temperature to 100 °C the yield of **5a** was not altered (entry 4, 5, Table 1). Obviously, the

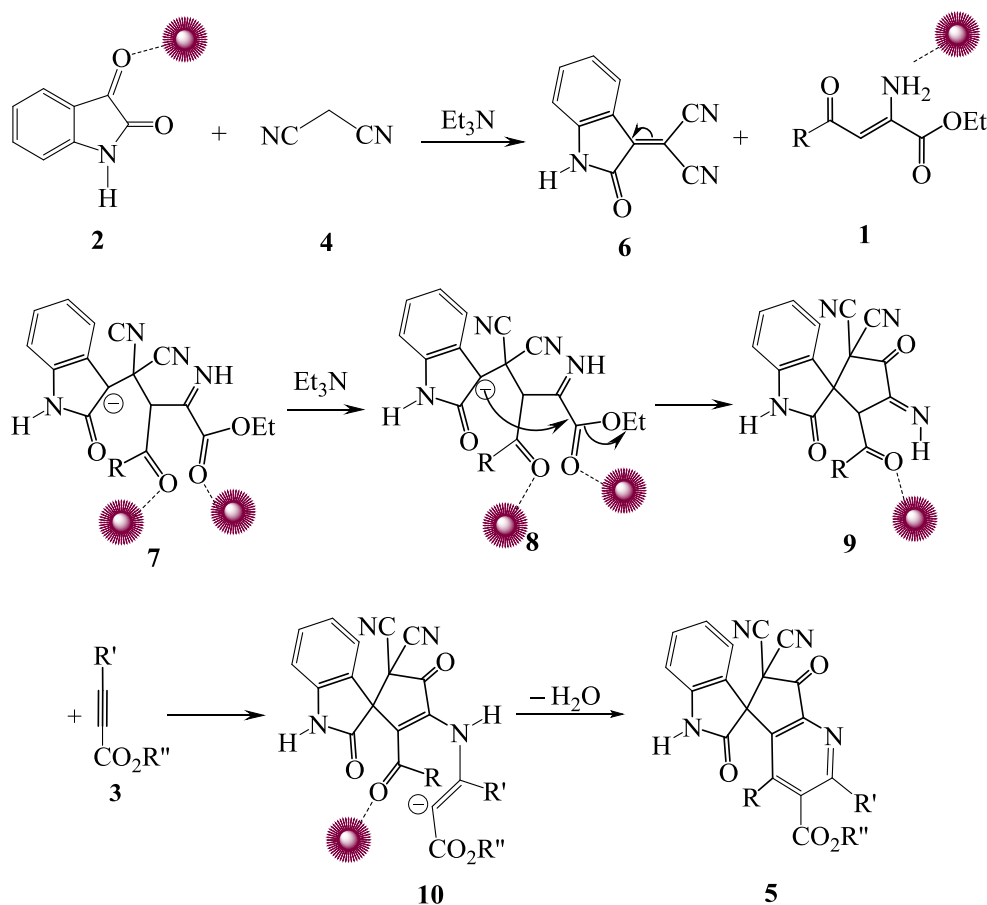
yield of product **5a** was obtained in 95 % yield after 3 h (entry 17, Table 1) in the best conditions. As shown in Table 1, the Ag/TiO₂/Fe₃O₄@MWCNTs MNCs (10 mol%) as catalyst, H₂O as and room temperature are the best conditions for preparation of **5a**. The outcomes in Table 2 displayed the Ag/TiO₂/Fe₃O₄@MWCNTs MNCs were employed five times in sample reaction (the preparation of spiro pyridine **5a**) without any significant variations in the yield of **5a**. The catalyst was separated after each run, washed with water, dried at environment temperature and used again in model reaction for confirmation the reusability of catalyst.

Table 2: Reusability of Ag/TiO₂/Fe₃O₄@MWCNTs MNCs in the synthesis of compound **5a**

| Run | 1 | 2 | 3 | 4 | 5 | 6 |
|------------------------------|----|----|----|----|----|----|
| Compound 6a yield (%) | 95 | 95 | 95 | 90 | 90 | 85 |

IR, ¹H NMR, ¹³C NMR, and mass spectral data are used for investigation and confirmation the structures of spiro pyridines **5**. For instance, the ¹H NMR spectrum of **5a** displayed three singlets at δ= 3.78, 3.83 and 3.87 ppm for methoxy protons, one singlet at 10.32 ppm for NH proton along with signals for aromatic protons at 6.98-8.22 ppm. The carbonyl group resonance of **5a** was detected at δ 164.2, 165.2, 167.3 and 187.2 ppm in the ¹³C NMR spectrum. The characteristic C=O bands was shown in IR spectrum of **5a** and the mass spectrum of **5a** was displayed the molecular ion peak at m/z = 522. Although there aren't any records for the details of reaction mechanism, the

suggested mechanism for these reactions is investigated in Scheme 2. It is supposable that the reaction begins with the reaction of enamin **1** with addition product of isatin **2** and malononitrile **4** in the presence of Ag/TiO₂/Fe₃O₄@MWCNTs MNCs as catalyst and Et₃N. The intermolecular cyclization of **7** produced **9** that react with activated acetylenic compounds **3** and produce intermediate **10** that by intermolecular cyclization along with elimination of water produce compounds **5**.



Scheme 2: Plausible mechanism for the production of 5

Conclusions

The $\text{Ag}/\text{TiO}_2/\text{Fe}_3\text{O}_4/\text{MWCNTs}$ MNCs as a new heterogeneous nanocatalyst was prepared and characterized using XRD, FESEM, EDX and TEM analyses. The performance of nanocatalyst was tested by carry out the one-pot synthesis of a new family of substituted spiropyridines via the condensation reactions of enamins, isatin, malononitrile and dimethyl acetylenedicarboxylate in the presence of Et_3N and synthesized catalyst in water at room temperature. The advantages of this procedure are: the one-pot operation, excellent yields of product in short reaction time, abundant and eco-friendly of catalyst. High atom economy and yield, mild and clean reaction condition, low catalyst loading, and short reaction time are some advantages of this procedure for synthesis of spiropyridines.

Experimental

General

All materials employed in this work were purchased from Fluka and Merck with no further purification. The structure of $\text{Ag}/\text{TiO}_2/\text{Fe}_3\text{O}_4/\text{MWCNTs}$ MNCs was confirmed by XRD, SEM, EDX and. X-ray diffraction patterns (XRD) was performed for calculating of the size of prepared $\text{Ag}/\text{TiO}_2/\text{Fe}_3\text{O}_4/\text{MWCNTs}$ MNCs. The Scherrer's formula; $D = 0.9\lambda/\beta \cos\theta$ used for calculating the average crystallite size of $\text{Ag}/\text{TiO}_2/\text{Fe}_3\text{O}_4/\text{MWCNTs}$ MNCs, where D is the diameter of the nanoparticles, λ ($\text{CuK}\alpha$) = 1.5406 Å and β is the full-width at half-maximum of the diffraction lines. FT-IR spectra were recorded by a Shimadzu IR-460 spectrophotometer for synthesized compounds. Also, the ^1H and ^{13}C NMR spectra are used for confirmation the structure of synthesized compounds by BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz respectively using TMS as the internal standard or 85%

H₃PO₄ as the external standard for solution in CDCl₃. A FINNIGAN-MAT 8430 spectrometer with an ionization potential of 70 eV utilized for Mass spectra. The elemental analysis C, H, and N for synthesized compounds was carried out by a Heraeus CHN-O-Rapid analyzer. Energy-dispersive X-ray Spectroscopy (EDX) was performed by Mira 3-XMU FESEM (Tescan Co, Brno, Czech Republic).

Preparation of TiO₂/Fe₃O₄MNPs

Tetraethylorthotitanat (1.5 g) and FeCl₂.4H₂O (1.5 g) was solved in *Petasites hybridus* rhizome water extract (30 mL) at 100 °C in round bottom flask for 5 h. Then it was cooled to room temperature, sonicated for 30 min and were centrifuged at 7000 rpm for about 10 min for removing the unwanted organic matters and then were filtered. The precipitate was filtered and cleaned with distilled water and ethanol (96%) for several times. The samples were then heated at 300 °C for 1 h. Produced bio-TiO₂/Fe₃O₄ MNPs was dried in the air at room temperature during 24 h.

Synthesis of Ag/TiO₂/Fe₃O₄MNCs:

In a typical method, 0.1 g of prepared TiO₂/Fe₃O₄ MNPs and AgNO₃ (1.5 g) and was dispersed in 100 mL *Petasites hybridus* rhizome water extract and the mixture was sonicated at 100 °C for 45 min. After cooling at r.t., the product was washed several times with water and ethanol respectively and separated with external magnetic field to afford the Ag/TiO₂/Fe₃O₄ MNPs.

Synthesis of Ag/TiO₂/Fe₃O₄@MWCNTs MNPs:

In a typical method, 0.1 g of prepared TiO₂/Fe₃O₄ MNPs, AgNO₃ (1.5 g) and multi walled carbon nanotubes (MWCNTs) (0.1 g) was dispersed in 100 mL *Petasites hybridus* rhizome water extract and the mixture was sonicated at 100 °C for 45 min. After cooling at r.t., the product was washed several times with water and ethanol respectively and separated with external magnetic field to afford the Ag/TiO₂/Fe₃O₄@MWCNT MNPs.

General procedures for the preparation of (5a-5j):

The mixture of enamin **1** (1 mmol), isatin **2** (1 mmol) and malononitrile **5** (1 mmol) was stirred for 45 min

in the presence of Ag/TiO₂/Fe₃O₄@MWCNTs MNPs as catalyst and Et₃N (10 mol%) in water at room temperature. After this time, activated acetylenic compounds **3** (1 mmol) was added to last mixture of reaction and new mixture was stirred for 1 h. After completion of reaction that was monitored by (TLC control (hexane–AcOEt, 5:1), the solid was separated by filtration and washed with EtOAc (Ethylacetate) for separating of catalyst. Then the column chromatography [silica gel (230–240 mesh; Merck), hexane/EtOAc 6:1] employed for purification of the residue to afforded pure title compounds.

Dimethyl 6,6-dicyano-4-(4-methoxyphenyl)-2',7-dioxo-6,7-dihydrospiro[cyclopenta [b]pyridine-5,3'-indoline]-2,3-dicarboxylate (5a):

Pale yellow powder, m.p. 132-134 °C, Yield: 0.99 g (95%). IR (KBr) (ν_{max}/cm⁻¹): 3345, 2198, 1735, 1725, 1589, 1478, 1386 and 1295 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ ppm: 3.78 (3 H, s, MeO), 3.83 (3 H, s, MeO), 3.87 (3 H, s, MeO), 6.98 (2 H, d, ³J = 7.8 Hz, 2 CH), 7.38 (1 H, d, ³J_{HH} = 7.6 Hz, CH), 7.42 (1 H, t, ³J = 7.6 Hz, CH), 7.56 (1 H, t, ³J = 7.6 Hz, CH), 7.67 (2 H, d, ³J = 7.8 Hz, 2 CH), 8.22 (1 H, d, ³J = 7.6 Hz, CH), 10.32 (1 H, s, NH). ¹³C NMR (125.7 MHz, CDCl₃): δ 51.2 (MeO), 52.4 (MeO), 55.7 (MeO), 58.2 (C), 59.6 (C), 110.6 (CH), 111.5 (CN), 112.3 (CN), 113.6 (2 CH), 119.5 (2 CH), 120.3 (C), 121.2 (CH), 123.4 (CH), 131.2 (CH), 135.2 (C), 136.4 (CH), 140.2 (C), 146.3 (C), 147.2 (C), 150.6 (C), 152.3 (C), 156.3 (C), 164.2 (C=O), 165.2 (C=O), 167.3 (C=O), 187.2 (C=O). EIMS (70 eV): m/z (%) = 522 (15) M⁺, 491 (68) [M-31]⁺, 31 (100) [M-491]⁺. Anal. Calcd for C₂₈H₁₈N₄O₇ (522.47): C, 64.37; H, 3.47; N, 10.72. Found: C, 64.52; H, 3.63; N, 10.93 %.

Dimethyl 6,6-dicyano-4-(4-methylphenyl)-2',7-dioxo-6,7-dihydrospiro[cyclopenta [b] pyridine-5,3'-indoline]-2,3-dicarboxylate (5b):

Pale yellow powder, m.p. 128-130 °C, Yield: 0.96 g (95%). IR (KBr) (ν_{max}/cm⁻¹): 3352, 2234, 1738, 1726, 1587, 1486, 1354 and 1283 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ ppm: 2.27 (3 H, s, Me), 3.78 (3 H, s, MeO), 3.83 (3 H, s, MeO), 7.28 (1 H, d, ³J = 7.7 Hz, CH), 7.36 (1 H, t, ³J_{HH} = 7.6 Hz, CH), 7.45 (1 H, t, ³J = 7.6 Hz, CH), 7.58 (2 H, d, ³J = 7.8 Hz, 2 CH), 7.96 (2 H, d, ³J = 7.8 Hz, 2 CH), 8.24 (1 H, d, ³J = 7.6 Hz, CH), 10.43 (1 H, s, NH). ¹³C NMR (125.7 MHz, CDCl₃): δ 21.6 (Me), 51.8 (MeO), 52.6 (MeO), 58.3 (C), 59.7

(C), 110.7 (CH), 111.8 (CN), 112.6 (CN), 119.2 (C), 121.3 (CH), 123.5 (CH), 126.4 (2 CH), 131.2 (2 CH), 132.3 (CH), 133.2 (C), 134.5 (C), 136.2 (C), 140.7 (C), 143.2 (C), 146.5 (C), 147.2 (C), 150.3 (C), 163.2 (C=O), 164.7 (C=O), 165.6 (C=O), 186.2 (C=O). EIMS (70 eV): m/z (%) = 506 (10) M⁺., 475 (78) [M-31] +., 31 (100) [M-475] +.. Anal. Calcd for C₂₈H₁₈N₄O₆ (506.47): C, 66.40; H, 3.58; N, 11.06. Found: C, 66.52; H, 3.72; N, 11.18 %.

Dimethyl 6,6-dicyano-4-(4-ethylphenyl)-2',7-dioxo-6,7-dihydrospiro[cyclopenta [b] pyridine-5,3'-indoline]-2,3-dicarboxylate (5c):

Pale yellow powder, m.p. 135-137 °C, Yield: 0.96 g (92%). IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3358, 2237, 1742, 1728, 1593, 1487, 1357 and 1292 cm^{-1} . ¹H NMR (500 MHz, CDCl₃): δ ppm: 1.32 (3 H, t, ³J_{HH} = 7.4 Hz, Me), 2.86 (2 H, q, ³J_{HH} = 7.4 Hz, CH₂), 3.75 (3 H, s, MeO), 3.86 (3 H, s, MeO), 7.23 (2 H, d, ³J = 7.8 Hz, 2 CH), 7.32 (1 H, d, ³J_{HH} = 7.6 Hz, CH), 7.43 (1 H, t, ³J = 7.6 Hz, CH), 7.52 (1 H, t, ³J = 7.6 Hz, CH), 7.89 (2 H, d, ³J = 7.8 Hz, 2 CH), 8.26 (1 H, d, ³J = 7.6 Hz, CH), 11.23 (1 H, s, NH). ¹³C NMR (125.7 MHz, CDCl₃): δ 15.6 (Me), 28.6 (CH₂), 51.6 (MeO), 52.4 (MeO), 58.4 (C), 59.8 (C), 110.5 (CH), 111.3 (CN), 112.5 (CN), 119.3 (C), 121.5 (CH), 123.6 (CH), 126.5 (2 CH), 131.3 (CH), 133.2 (C), 136.2 (2 CH), 137.3 (C), 140.2 (C), 143.2 (C), 144.5 (C), 147.2 (C), 148.3 (C), 150.5 (C), 163.5 (C=O), 164.8 (C=O), 165.8 (C=O), 188.3 (C=O). EIMS (70 eV): m/z (%) = 520 (10) M⁺., 489 (68) [M-31] +., 31 (100) [M-489] +.. Anal. Calcd for C₂₉H₂₀N₄O₆ (520.49): C, 66.92; H, 3.87; N, 10.76. Found: C, 67.12; H, 3.96; N, 10.93 %.

Diethyl 6,6-dicyano-4-(4-methylphenyl)-2',7-dioxo-6,7-dihydrospiro[cyclopenta [b] pyridine-5,3'-indoline]-2,3-dicarboxylate (5d):

Pale yellow powder, m.p. 145-147 °C, Yield: 0.96 g (90%). IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3363, 2287, 1742, 1727, 1596, 1487, 1356 and 1288 cm^{-1} . ¹H NMR (500 MHz, CDCl₃): δ ppm: 1.12 (3 H, t, ³J = 7.4 Hz, Me), 1.28 (3 H, t, ³J = 7.4 Hz, Me), 2.25 (3 H, s, Me), 4.12 (2 H, q, ³J = 7.4 Hz, CH₂O), 4.26 (2 H, q, ³J = 7.4 Hz, CH₂O), 7.26 (1 H, d, ³J = 7.6 Hz, CH), 7.32 (1 H, t, ³J_{HH} = 7.6 Hz, CH), 7.43 (1 H, t, ³J = 7.6 Hz, CH), 7.54 (2 H, d, ³J = 7.8 Hz, 2 CH), 8.03 (2 H, d, ³J = 7.8 Hz, 2 CH), 8.16 (1 H, d, ³J = 7.6 Hz, CH), 11.34 (1 H, s, NH). ¹³C NMR (125.7 MHz, CDCl₃): δ 13.9 (Me), 14.2 (Me), 22.3 (Me), 58.5 (C), 60.2 (C), 61.2 (CH₂O), 62.4

(CH₂O), 110.5 (CH), 110.6 (CN), 111.6 (CN), 119.5 (C), 121.6 (CH), 123.2 (CH), 125.7 (2 CH), 131.5 (2 CH), 132.4 (CH), 133.5 (C), 134.6 (C), 136.4 (C), 140.2 (C), 143.5 (C), 146.6 (C), 147.3 (C), 149.3 (C), 163.8 (C=O), 164.6 (C=O), 165.7 (C=O), 187.9 (C=O). EIMS (70 eV): m/z (%) = 534 (15) M⁺., 489 (86) [M-45] +., 45 (100) [M-489] +.. Anal. Calcd for C₃₀H₂₂N₄O₆ (534.52): C, 67.41; H, 4.15; N, 10.48. Found: C, 67.62; H, 4.28; N, 10.63 %.

Methyl 6,6-dicyano-2',7-dioxo-4-(p-tolyl)-6,7-dihydrospiro[cyclopenta[b]pyridine-5,3'-indoline] -3-carboxylate (5e):

Pale yellow powder, m.p. 116-118 °C, Yield: 0.81 g (90%). IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3373, 2268, 1743, 1725, 1586, 1494, 1367 and 1292 cm^{-1} . ¹H NMR (500 MHz, CDCl₃): δ ppm: 2.32 (3 H, s, Me), 3.83 (3 H, s, MeO), 7.32 (1 H, d, ³J = 7.6 Hz, CH), 7.42 (1 H, t, ³J_{HH} = 7.6 Hz, CH), 7.52 (1 H, t, ³J = 7.6 Hz, CH), 7.62 (2 H, d, ³J = 7.8 Hz, 2 CH), 7.95 (2 H, d, ³J = 7.8 Hz, 2 CH), 8.12 (1 H, d, ³J = 7.6 Hz, CH), 8.68 (1 H, s, CH), 10.86 (1 H, s, NH). ¹³C NMR (125.7 MHz, CDCl₃): δ 21.8 (Me), 51.6 (MeO), 59.4 (C), 60.4 (C), 110.2 (CH), 110.8 (CN), 111.7 (CN), 120.3 (CH), 122.5 (C), 123.6 (CH), 126.7 (2 CH), 130.2 (C), 131.5 (CH), 132.7 (CH), 133.8 (2 CH), 134.2 (C), 139.5 (C), 140.2 (C), 141.8 (C), 146.3 (C), 156.8 (C), 166.5 (C=O), 167.3 (C=O), 185.8 (C=O). EIMS (70 eV): m/z (%) = 448 (15) M⁺., 417 (84) [M - 31] M⁺., 31 (100) [M-417] +.. Anal. Calcd for C₂₆H₁₆N₄O₄ (448.43): C, 69.64; H, 3.60; N, 12.49. Found: C, 69.75; H, 3.72; N, 12.63 %.

Methyl 6,6-dicyano-2',7-dioxo-4-(4-methoxyphenyl)-6,7-dihydrospiro [cyclopenta[b] pyridine -5,3'-indoline]-3-carboxylate (5f):

Pale yellow powder, m.p. 124-126 °C, Yield: 0.85 g (92%). IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3362, 2298, 1742, 1727, 1593, 1486, 1378 and 1286 cm^{-1} . ¹H NMR (500 MHz, CDCl₃): δ ppm: 3.78 (3 H, s, MeO), 3.85 (3 H, s, MeO), 6.98 (2 H, d, ³J = 7.8 Hz, 2 CH), 7.36 (1 H, d, ³J = 7.6 Hz, CH), 7.45 (1 H, t, ³J_{HH} = 7.6 Hz, CH), 7.56 (1 H, t, ³J = 7.6 Hz, CH), 7.68 (2 H, d, ³J = 7.8 Hz, 2 CH), 8.19 (1 H, d, ³J = 7.6 Hz, CH), 8.23 (1 H, s, CH), 10.92 (1 H, s, NH). ¹³C NMR (125.7 MHz, CDCl₃): δ 52.6 (MeO), 55.7 (MeO), 58.6 (C), 59.6 (C), 110.3 (CH), 111.2 (CN), 112.5 (CN), 116.5 (2 CH), 118.6 (2 CH), 121.2 (CH), 122.5 (C), 123.4 (CH), 130.4 (C), 131.7 (CH), 134.3 (C), 139.5 (C), 140.3 (C), 142.5 (C), 145.8 (C), 156.2 (C), 158.2 (CH), 165.6

(C=O), 168.2 (C=O), 186.5 (C=O). EIMS (70 eV): m/z (%) = 464 (15) M+, 433 (68) [M-31] +, 31 (100) [M-433] +. Anal. Calcd for C₂₆H₁₆N₄O₅ (464.43): C, 67.24; H, 3.47; N, 12.06. Found: C, 67.36; H, 3.62; N, 12.18 %.

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