

Proceeding Paper

Efficient and Green Synthesis of Acridinedione Derivatives Using Highly Fe_3O_4 @Polyaniline- SO_3H as Efficient Heterogeneous Catalyst[†]

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Abstract: In the present investigation, an efficient heterogeneous catalyst system made of a polyaniline-derived polymer (Poly [anthranilic acid]-[N-(1',3'-phenylenediamino) –3-butane sulfonate]) and iron oxide nanoparticles (Fe_3O_4 NPs) is presented. Firstly, this novel catalytic system (Fe_3O_4 @Polyaniline- SO_3H) has been fabricated via a convenience method and magnetized via an in situ process. The as-prepared solid acid catalyst was also carefully analyzed by Fourier transfer infrared spectroscopy (FTIR) and energy-dispersive X-ray spectroscopy (EDX). It has been suitably applied for the one-pot multicomponent synthesis of acridinediones as an important class of heterocyclic compounds. The first and foremost advantage of this catalytic system is that the (Fe_3O_4 @Polyaniline- SO_3H) is magnetically separated from the reaction mixture through their high paramagnetic behavior. The main attractive characteristics of the presented green protocol are very short reaction times, excellent yields, and the avoidance of hazardous or toxic reagents and solvents. Easy separation, high reusability, cost-effective and mild catalyst are important advantages of the new catalyst in comparison to other catalysts for the synthesis of acridinedione derivatives via one-pot four-component reaction.

Keywords: heterogeneous catalyst; acridinedione derivatives; reusability



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1. Introduction

Multi-component reaction (MCR) consists of three or more substances and is an easy and environmentally friendly process that has received much attention due to its wide range of applications in medicinal chemistry [1]. Different multicomponent reactions like Mannich, Biginelli, Strecker, Hantzsch, and acridinedione derivatives are significant transformations for the synthesis of pharmaceutical compounds [2]. Acridinediones are a highly important class of organic compounds since they possess a wide range of pharmaceutical and biological activities such as a positive inotropic effect promoting the entry of calcium to the intracellular space, anticancer activity, enzyme and tumor cell inhibition, antimicrobial activity and cytotoxicity [3]. They have structural similarities to 1,4-dihydropyridines (1,4-DHPs), which are well-known intermediates in the synthesis of several pharmaceuticals [4]. Acridinedione derivatives are synthesized with different methods, which usually involve hazardous solvents, expensive reagents, and high reaction times. Heterogeneous catalysts have a crucial role in determining the condition of reactions [5,6]. They are known as compounds or substances that accelerate a chemical reaction without change. The advantages of heterogeneous catalysts are high activity, high surface area, thermal stability, selectivity and non-toxicity [7].

In recent years, various methods for the synthesis of acridinedione derivatives using three components of 5,5-dimethyl-1,3-cyclohexanedione (dimedone), aromatic aldehydes

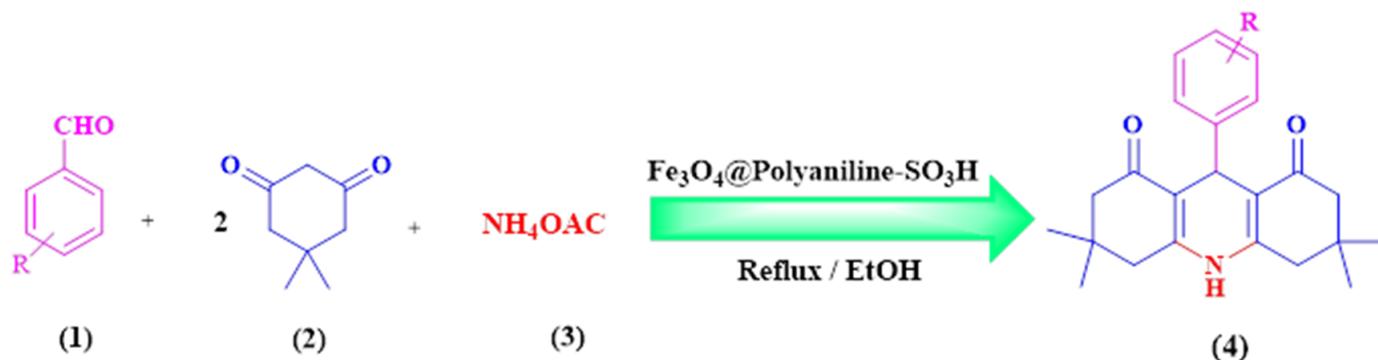
and various types of aniline or ammonium acetate in the presence of various catalysts such as $\text{Fe}_3\text{O}_4@\text{SiO}_2@\text{Ni-Zn-Fe}$ LDH [8], $\text{Fe}^{3+}/4\text{A}$ molecular sieves [4], GO/CR- Fe_3O_4 NPs [9], graphene oxide incorporated strontium magnetic nanocatalyst (MSrGO NCs) [10], graphene oxide decorated with platinum nanoparticles (Pt NPs@GO) [10], nano-ordered 1,3,5-tris(2-hydroxyethyl) isocyanurate-1,3-propylene covalently functionalized MCM-41 (MCM-41-Pr-THEIC) [11], vitamin B1 [12], sulfuric acid-modified poly(vinylpyrrolidone) ((PVP- SO_3H) HSO_4) [13], Bi_2O_3 nanoparticles [14] and pumice supported sulfonic acid (pumice@ SO_3H) [15] have been reported.

Although the reported methods have their own advantages and limitations, the use of a heterogeneous catalyst with reusability is more important in the synthesis of organic compounds.

Magnetic nanoparticles have received much attention due to their easy recycling ability in synthetic chemistry. However, magnetic nanoparticles with a large surface area, which leads to a high load capacity of catalysts, have found many applications. Magnetic nanoparticles, especially iron oxide nanoparticles, due to their suitable properties for catalytic and environmental processes, were considered to be a solid substrate for the immobilization of catalysts [1]. Organic catalysts can be easily activated on the surface of iron oxide nanoparticles and after the reaction, they can be easily separated from the reaction medium and the problem of separating the catalyst from the reaction mixture can be solved [16–18].

In this study, an acidic magnetic catalyst consisting of a polyaniline-derived copolymer and Fe_3O_4 NPs was prepared and used as a recyclable heterogeneous catalyst for the synthesis of acridindione derivatives.

The present catalytic system has several remarkable advantages such as short reaction times (10–15 min), excellent yields, low environmental impact, and moderate reaction conditions. The prepared solid acid catalyst can be easily removed from the reaction using a permanent magnet and recovered in excellent purity for direct reuse (Scheme 1).



Scheme 1. $\text{Fe}_3\text{O}_4@\text{Polyaniline-SO}_3\text{H}$ -catalyzed synthesis of acridindione derivatives through multi-component reaction of aldehyde derivatives (1), dimedone (2) and ammonium acetate (3) in EtOH under reflux conditions.

2. Experimental

2.1. General

All reagents were purchased from Fluka and Merck companies and used without further purification. Thin-layer chromatography (TLC) was used for the purity determination of substrates, products and reaction monitoring over silica gel 60 F254 aluminum sheet. Melting points were measured in open capillary tubes with Electro thermal 9100 melting point apparatus. The FT-IR spectra were measured with a Shimadzu IR-100 spectrometer, and the energy-dispersive X-ray (EDX) spectrum was recorded on Numerix DXP-X10P. ^1H and ^{13}C NMR spectra of the products were measured with a Bruker Ascend 400 MHz spectrometer.

2.2. Synthesis of *N*-(1',3'-Phenylenediamino) –3-Butane Sulfonate

N-(1',3'-phenylenediamino) –3-butane sulfonate was synthesized based on a previously reported [19]. In a typical synthesis, 1,3-propane sultone (3.06 g, 25.1 mmol) was added to a solution of *m*-phenylenediamine (2.71 g, 25.1 mmol) in tetrahydrofuran (50.0 mL), and the mixture was refluxed and agitated for 24 h under N₂ atmosphere. The reaction mixture was cooled to room temperature and the resultant precipitate, collected on a glass filter, was washed with a mixture of 500 mL of THF: methylene chloride 1:1 (*v/v*), and dried under vacuum to obtain a bluish-gray powder (4.98 g, 87% yield).

2.3. Synthesis of Poly [Anthranilic Acid]_{0.5}-[*N*-(1',3'-Phenylenediamino) –3-Butane Sulfonate]_{0.5}

The polyaniline-derived copolymer was synthesized according to the modified procedure reported [19]. In a typical reaction, Anthranilic acid (3.43 g, 25.01 mmol) and *N*-(1,3-phenylenediamino) –3-propane sulfonate (5.75 g, 25.00 mmol) were dissolved in a mixture containing 300 mL of 0.2 M HCl solution and 100 mL of ethanol. Ammonium persulfate (APS, 14.21 g, 62.2 mmol), dissolved in 200 mL of 0.2 M HCl solution, was then added to the above solution over 10 min, and the mixture was stirred for 24 h. After 24 h, 3.6 L of acetone was added to the solution to obtain a PANi polymer precipitate, which was centrifuged at 4000 rpm for 1 h to separate the precipitate. The precipitate was washed three times with a mixed solution of acetone/0.2 M HCl (6:1 *v/v*), and dried under vacuum to obtain 6.12 g of poly [anthranilic acid]_{0.5}-[*N*-(1',3'-phenylenediamino) –3-butane sulfonate]_{0.5} (PANi, 66.4% yield).

2.4. Synthesis of Fe₃O₄@Polyaniline-SO₃H Nanocomposite

In a three-necked round-bottom flask (250 mL), Fe₃O₄@Polyaniline-SO₃H (0.45 g) was well dispersed in DI water (100 mL) via ultrasonication (10 min). Then, a mixture of FeCl₃.6H₂O (0.2 g) and FeCl₂.4H₂O (0.1 g) was added to the flask and stirred for 30 min at 50 °C in a neutral atmosphere (N₂ gas). Next, the mixture was heated up to 70 °C, and NH₃ aqueous solution (1 M) was added dropwise until pH = 12 was obtained. After completion of the addition, the stirring was continued for an additional 2 h at 70 °C, then the product was magnetically separated, washed with DI water, and dried at 60 °C.

2.5. General Procedure for the Preparation of Acridinediones Derivatives

Ammonium acetate (1.0 mmol,) dimedone (2.0 mmol,) aromatic aldehyde (1.0 mmol), ethanol (5.0 mL), and Fe₃O₄@Polyaniline-SO₃H nanocomposite (30.0 mg) were mixed in a round bottom flask. They were stirred under reflux conditions for an appropriate time. After completing the reaction (monitored by TLC), the magnetic nanocatalyst was magnetically separated and the desired product was isolated by DMF.

3. Results and Discussion

The as-prepared Fe₃O₄@Polyaniline-SO₃H nanocatalyst was analyzed using different spectroscopic methods as well as including FTIR and EDX.

The FTIR spectrum of Fe₃O₄@Polymer is shown in Figure 1. The nanocatalyst Fe₃O₄@Polyaniline-SO₃H shows an adsorption band in the 3432 cm⁻¹ region that is due to the presence of both OH and NH groups. Furthermore, the adsorption band corresponding to C-H bonds is observed around 2928 cm⁻¹. Furthermore, the adsorption band in the region of 1684 cm⁻¹ is attributed to the symmetric vibrations of C=O of the carboxyl (COOH) groups. On the other hand, the characteristic band observed at 1382 and 1034 cm⁻¹ are assigned to the asymmetric and symmetric S=O stretching vibration of the SO₃H group. In addition, the observed adsorption band at 522 cm⁻¹ is attributed to the stretching vibrations of Fe-O.

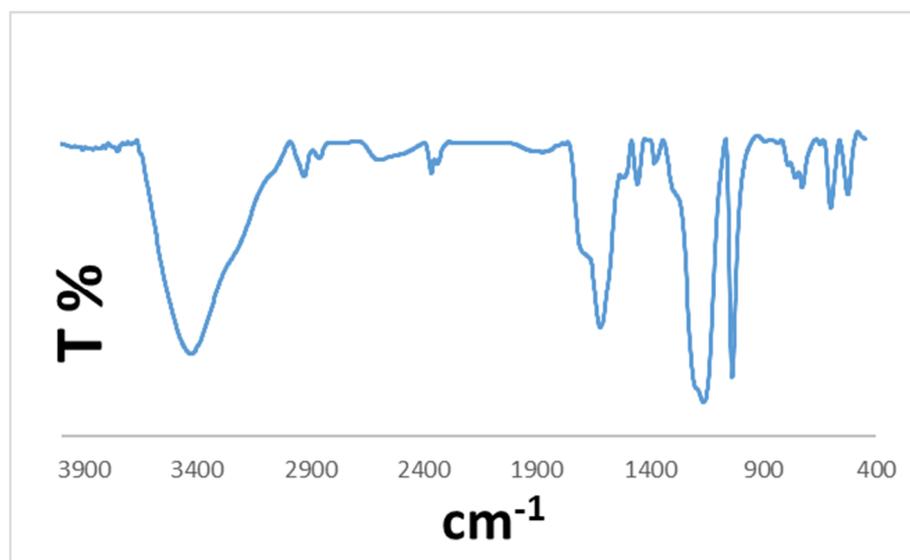


Figure 1. FTIR spectra of the Fe_3O_4 @Polymer.

As shown in Figure 2, the EDX spectra of the Fe_3O_4 @Polyaniline- SO_3H verified the presence of C (11.65 %), N (5.45 %), O (36.95 %), S (2.96 %), and Fe (42.99 %), respectively.

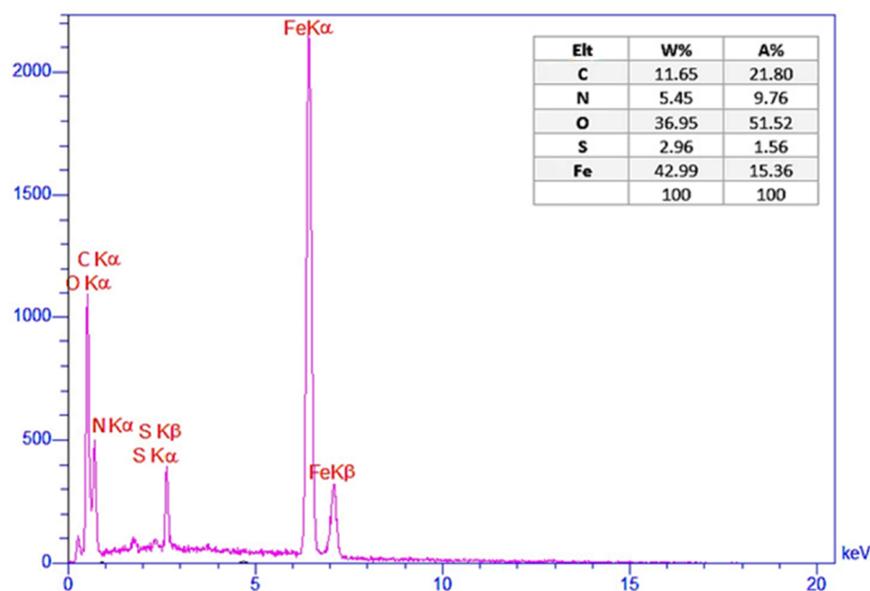


Figure 2. EDX spectra of the Fe_3O_4 @Polyaniline- SO_3H .

In order to monitor the catalytic performance of the fabricated Fe_3O_4 @Polyaniline- SO_3H nanocomposite, the reaction conditions were initially optimized by using various catalytic ratios in different reaction times, for the synthesis of 3,3,6,6-tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**4a**) as a model compound. For this aim, benzaldehyde **1** (1 mmol), ammonium acetate **2** (1 mmol), and dimedone **3** (2 mmol) were used (Scheme 1). The reaction progress was also monitored by TLC. It was observed that 30 mg of Fe_3O_4 @Polyaniline- SO_3H nanocomposite in ethanol during a 10 min stirring would provide the optimal conditions for product **4a** synthesis reactions. Furthermore, the catalytic role of the prepared Fe_3O_4 @Polyaniline- SO_3H nanocomposite was more investigated in further synthesis reactions of acridinedione derivatives (**4b4g**), as reported in Table 1. As can be observed, high reaction yields have been obtained in short reaction times by using a partial amount of this catalytic system.

Table 1. The synthesis of acridinedione derivatives in the presence of Fe₃O₄@Polyaniline-SO₃H nanocomposite.

Entry	Aldehyd (R)	Product	Time (min)	Isolated Yield * (%)	Mp. (°C) Ref.
1	H	4a	10	98	189–191 [9]
2	3-OHC ₆ H ₄	4b	15	93	310–312 [9]
3	4-ClC ₆ H ₄	4c	12	92	244–246 [3]
4	3-NO ₂ C ₆ H ₄	4d	15	90	293–295 [3]
5	4-CH ₃ OC ₆ H ₄	4e	15	91	278–280 [11]
6	4-CH ₃ C ₆ H ₄	4f	12	94	>300 [11]
7	4-BrC ₆ H ₄	4g	15	96	253–255 [20]

* **Reaction conditions:** dimedone (2 mmol), aldehyde (1 mmol), ammonium acetate (1 mmol), catalyst (0.3 g). and EtOH (5 mL) under reflux conditions.

4. Conclusions

In conclusion, we have developed a facile and efficient protocol for the synthesis of acridinedione derivatives using Fe₃O₄@Polyaniline-SO₃H nanocomposite as a catalyst in aqueous ethanol as the solvent via one-pot-four-component condensation of aromatic aldehydes, dimedone, ammonium acetate. The significant advantages of this methodology are the reasonably simple experimental workup procedure and catalyst preparation, ease of product isolation, high to excellent yields, short reaction time, and the use of a catalytic amount of Fe₃O₄@Polyaniline-SO₃H nanocomposite. The nanocatalyst can be conveniently separated and recovered from the reaction system by a magnet and can be reused six times without detectable loss in catalytic activity.

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