

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 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-designed 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. As the first and foremost advantage of this catalytic system, this can be referred to 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, which is an easy and environmentally friendly process that has received much attention due to its wide range of applications in medicinal chemistry [1]. The different multicomponent reactions like Mannich, Biginelli, Strecker, Hantzsch, and acridinedione derivatives are significant transformation 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 ionotropic 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 similarity to 1,4-dihydropyridines (1,4-DHPs), which are well known intermediates in the synthesis of several pharmaceuticals [4]. Acridinedione derivatives synthesized with different methods, which usually suffer from hazard solvents, expensive reagents, and high reaction time. 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].

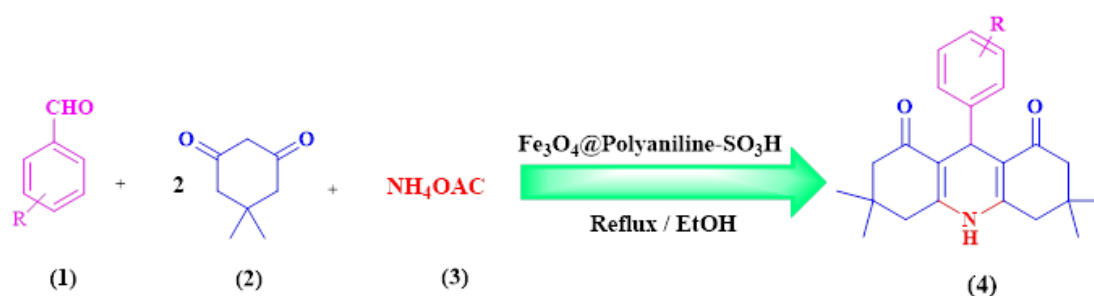
In recent years, various methods for the synthesis of acridindione derivatives using three components of 5,5-dimethyl-1,3-cyclohexanedione (dimedone), aromatic aldehydes and various types of aniline or ammonium acetate in the presence of various catalysts such as Fe₃O₄@SiO₂@Ni–Zn–Fe LDH [8], Fe³⁺/4 A molecular sieves [4], GO/CR-Fe₃O₄ 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–SO₃H)HSO₄) [13], Bi₂O₃ Nanoparticles [14] and pumice supported sulfonic acid (pumice@SO₃H) [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 large surface area, which leads to high load capacity of catalysts, have found many applications. Magnetic nanoparticles, especially iron oxide nanoparticles, due to suitable properties for catalytic and environmental processes, were considered as a solid substrate for immobilization of catalysts [1]. Organic catalysts can be easily activated on the surface of iron oxide nanoparticles and after the reaction, it can be easily separated from the reaction medium and the problem of separating the catalyst from the reaction mixture can be solved [16].

In this study, an acidic magnetic catalyst consisting of polyaniline derived copolymer and Fe₃O₄ 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, environmentally friendly, 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. Fe₃O₄@Polyaniline-SO₃H-catalyzed synthesis of acridindione derivatives through multicomponent 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 energy-dispersive X-ray (EDX) spectrum was recorded on Numerix DXP-X10P. ¹H and ¹³C 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, to a solution of *m*-phenylenediamine (2.71 g, 25.1 mmol) in tetrahydrofuran (50.0 mL) was added 1,3-propane sultone (3.06 g, 25.1 mmol), 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}

Polyaniline derived copolymer was synthesized according to 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) were added to the flask and stirred for 30 min, at 50 °C under 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 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 stirred under reflux condition for the appropriate time. After completing the reaction (monitored by TLC), 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 corresponded to C-H bonds are observed around 2928 cm⁻¹. Also, 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.

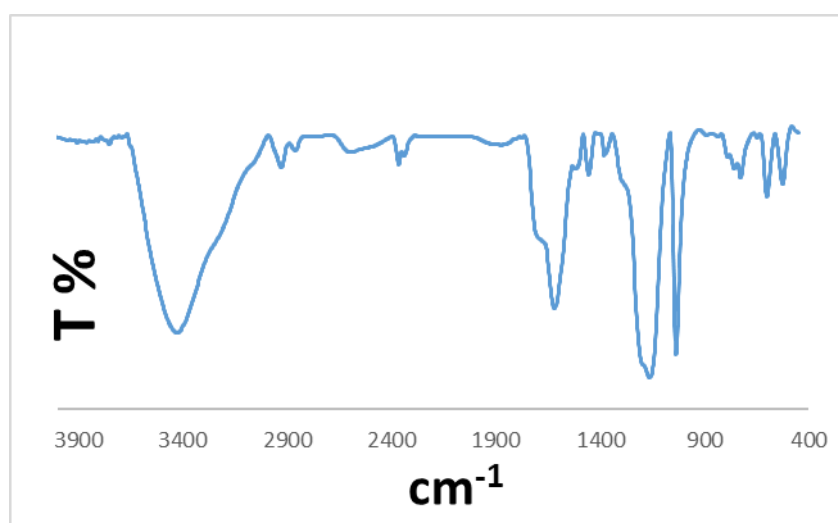


Figure 1. FTIR spectra of the Fe₃O₄@Polymer.

As shown in Figure 2, the EDX spectra of the Fe₃O₄@Polyaniline-SO₃H verified the presence of C (11.65 %), N (5.45 %), O (36.95 %), S (2.96 %), and Fe (42.99 %), respectively.

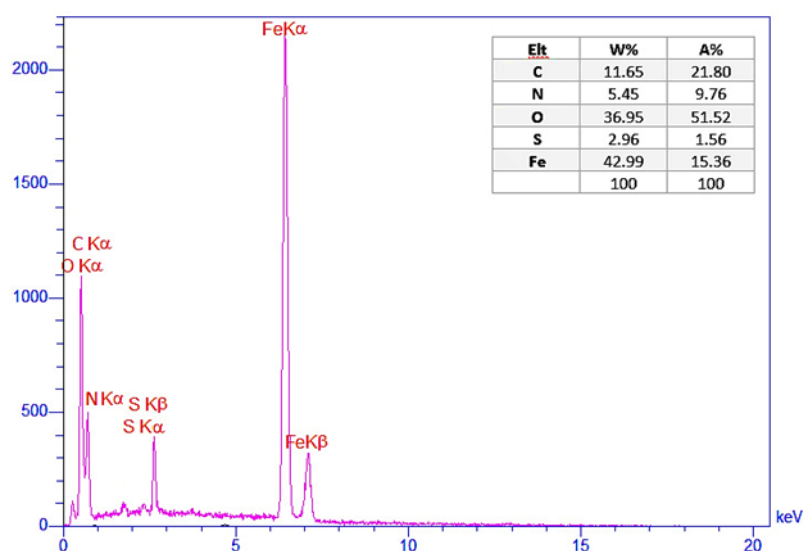


Figure 2. EDX spectra of the Fe₃O₄@Polyaniline-SO₃H.

In order to monitor the catalytic performance of the fabricated Fe₃O₄@Polyaniline-SO₃H nanocomposite, the reaction conditions were initially optimized through 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 Fe₃O₄@Polyaniline-SO₃H 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 Fe₃O₄@Polyaniline-SO₃H nanocomposite was more investigated in further synthesis reactions of acridinedione derivatives (**4b-4g**), as reported in Table 1. As can be observed, high reaction yields have been obtained in short reaction times through 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-CIC ₆ H ₄	4c	12	92	244–246 [3]
4	3-NO ₃ 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 an efficient protocol for the synthesis of acridinedione derivatives using Fe₃O₄@Polyaniline-SO₃H nanocomposite as a catalyst in aqueous ethanol as solvent via one-pot-four-component condensation of aromatic aldehydes, dimedone, ammonium acetate. Significant advantages of this study are reasonably simple experimental workup procedure and catalyst preparation, ease of product isolation, high to excellent yields, short reaction time and using catalytic amount of Fe₃O₄@Polyaniline-SO₃H nanocomposite, are notable advantages of the present methodology. The nanocatalyst can be conveniently separated and recovered from the reaction system by magnet and can be reused for six times without detectable loss in catalytic activity.

Institutional Review Board Statement:

Informed Consent Statement:

Data Availability Statement:

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