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Synthesis of Functionalized Thiopyrano [2,3-*b*]quinolines via Cascade Reactions Catalyzed by Magnetic Arginine/Alginate Biocomposite †

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Abstract: An effective synthesis of functionalized thiopyrano [2,3-*b*]quinolines has been described via cascade reactions using super paramagnetic iron oxide nanoparticles (SPIONs) coated with L-arginine (Arg) grafted alginate (Alg), called Fe_3O_4@Alg@CPTMS@Arg. The reaction was performed between commercially available CH acid compounds such as dimedone or malononitrile, and 2-mercapto-quinoline-3-carbaldehydes under green conditions. This efficient method provides a new route for the formation of functionalized three or four fused rings.

Keywords: L-arginine; alginate; superparamagnetic nanocomposite; 2-mercapto-quinoline-3-carbaldehydes; thiochromene derivatives

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1. Introduction

Nowadays, a major challenge in the preparation of effective medicinal compounds is to design well-organized methods based on the application of recyclable biocatalysts. Iron oxide (Fe_3O_4), due to prominent characteristics such as superparamagnetic properties, vast surface area, and low toxicity, has valuable consideration in the modification of biocompatible conditions [1]. Polymers which are modified by Fe_3O_4 are a good choice for catalyst applications [2,3]. Although there are many different types of polymers, among them, natural origin polymers have the most achievements today due to their environmentally friendly conditions [4]. Subdivisions of these natural polymers include polysaccharides, such as alginates originating from brown seaweed with alternating groups of (1→4) α-Lguluronic acid (G) and (1→4) β-D-mannuronic acid (M) units, with specific functional groups in its structure which have the ability to interact appropriately with other excellent compounds, including the amino acid arginine as a bi-functionalized natural polysaccharide, strikingly, playing the role of catalyst [5,6]. In continuation of our efforts in the optimal synthesis and evaluation of heterogeneous catalyst performance for outstanding pharmaceutical compounds, therefore, we report our results for a facile and convenient synthesis of thiopyrano [2,3-*b*]quinoline derivatives using arginine functionalized alginate as a highly efficient biocatalyst.

2. Experimental

2.1. Reagents and Apparatus

All commercial solvents and chemicals were purchased from Merck and Aldrich. Deionized water was used for all dilutions. The IR spectrum was recorded on a Shimadzu 470 FT-IR spectrometer. Ultrasound was performed by Alma at 60 Hz. The melting points of the samples were measured by melting point apparatus, Electrothermal IA 9100. The

^{1}H NMR and ^{13}C NMR spectra at 500 MHz and 125 MHz (^{13}C) were recorded on the Bruker DRX-500 Avance spectrometer, which is fully consistent with those reported in authentic samples or reported in the literature.

2.2. Synthesis of Fe_3O_4@Alg Nanoparticles

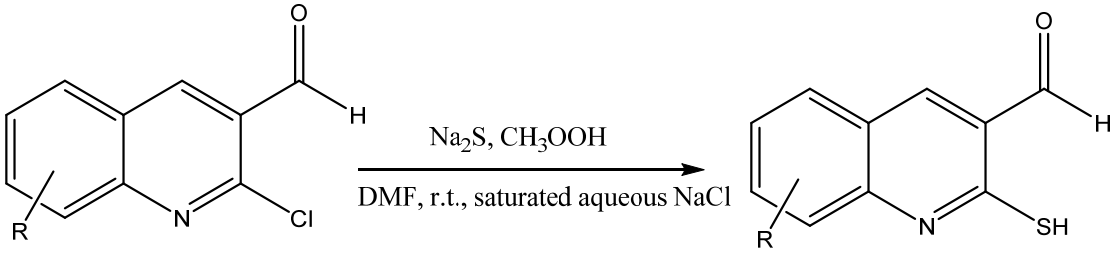
Fe_3O_4@Alg nanoparticles were prepared by the co-precipitation method. In order to synthesize the catalyst, a mixture of $FeCl_3 \cdot 6H_2O$ (4.68 g, 17.31 mmol), $FeCl_2 \cdot 4H_2O$ (2.3 g, 11.56 mmol) and sodium alginate (1 g), was stirred vigorously for 2 h using 50 mL of deionized water (DI) as a solvent in an inert atmosphere. After that, the pH of the solution was adjusted to 10 by the dropwise addition of aqueous ammonia solution (25%). The produced magnetic nanoparticles were separated by an external magnet, the solid procured was washed with H_2O and EtOH, and it was finally dried for 7 h at 100 °C to be used for the next step of catalysis synthesis.

2.3. Synthesis of Fe_3O_4@Alg@CPTMS@Arg

The mixture of Fe_3O_4@Alg nanoparticles (1.5 g), 3-chloropropyltrimethoxysilane (3 mL, 16.45 mmol), and dry toluene (20 mL) was dispersed under ultrasonic irradiation for 20 min to obtain a milky suspension. The solid was separated by an external magnet, washed with absolute ethanol, and then dried in an oven for 12 h. To a suspension of Fe_3O_4@Alg@CPTMS (1 g) in dry toluene, L-arginine (1.5 g, 8.61 mmol) and trimethylamine (0.07 g, 1.2 mmol) were added and refluxed for 48 h. Afterward, the obtained nanoparticles were separated by a magnet, washed with EtOH and DI, and then dried in a vacuum oven at 110 °C for 6 h to obtain Fe_3O_4@Alg@CPTMS@Arg.

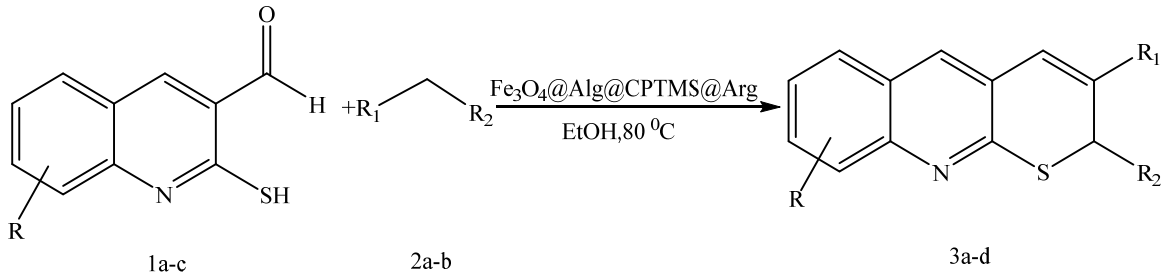
3. Results and Discussion

The ability of Fe_3O_4@Alg@CPTMS@Arg to synthesize 2-mercaptoquinoline-3-carbaldehyde was investigated in ethanol under reflux conditions. The synthesis of 2-mercaptoquinoline-3-carbhaldehyde derivatives was performed in two steps. In the first step, 2-chloroquinoline-3-carbaldehyde (4 mmol), sodium sulfide (16 mmol), and N,N-dimethylformamide (DMF, 10 mmol) were added to a round bottom flask and the mixture was vigorously stirred at room temperature (r.t.) for 2 h to obtain an orange solution. A saturated solution of sodium chloride (40 mL) was then added to the reaction mixture. Glacial acetic acid was gradually added to the reaction mixture to make the solution clear and to prevent further precipitation. Finally, the precipitate was filtered, washed with water, and dried at ambient temperature to prepare 2-mercaptoquinoline-3-carbhaldehyde (Scheme 1).



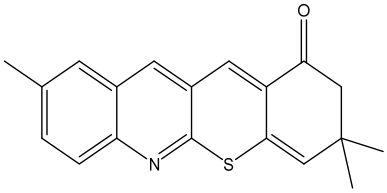
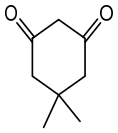
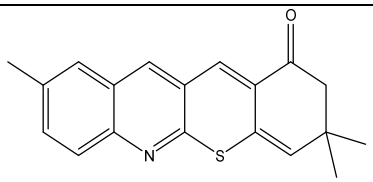
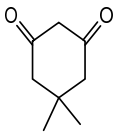
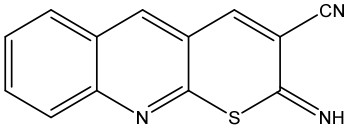
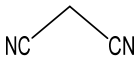
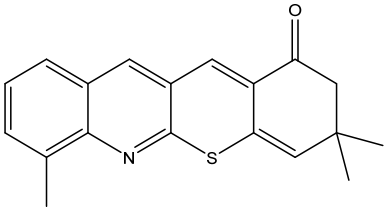
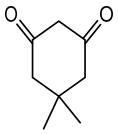
Scheme 1. Synthesis of 2-mercaptoquinoline-3-carbhaldehyde.

The catalytic activity of the as-prepared nanocomposite was studied in the synthesis of thiopyrano derivatives **3a–d** (Scheme 2). The reaction was investigated for CH acidic compounds **2a–b** and 2-mercaptoquinoline 3-carbaldehyde derivatives **1a–c**, and the results are shown in Table 1.



Scheme 2. Synthesis of thiopyran derivatives in the presence of Fe_3O_4@Alg@CPTMS@Arg.

Table 1. Synthesis of thiopyrano [2,3-*b*]quinolines by Fe_3O_4@Alg@CPTMS@Arg nanocatayst.

Entry	Product	CH-Acidic Compounds	Time (min)	Yield (%)	M.p. (°C) Found/Reported
1	 **3a**		40	75	192–194/192–194 [7]
2	 **3b**		35	60	140–143/139–141 [7]
3	 **3c**		30	80	156–158/156–158 [7]
4	 **3d**		30	65	200/197–199 [7]

4. Conclusions

In this work, the catalytic performance of super paramagnetic iron oxide nanoparticles (SPIONs) coated with L-arginine (Arg) grafted alginate, Fe_3O_4@Alg@CPTMS@Arg, has been investigated in the synthesis of thiopyrano [2,3-*b*]quinoline derivatives via a condensation reaction of 2-mercaptoquinoline 3-carbaldehydes and CH-acidic compounds under mild and green conditions necessary for the development of sustainable chemistry. This methodology has several benefits, including the recoverability of the catalyst, short reaction times, the elimination of toxic solvents, and high yields.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

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