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Synthesis of 4*H*-pyran derivatives via a green one-pot multicomponent reaction catalyzed by $CuFe_2O_4$ magnetic nanoparticles as a reusable catalyst

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Abstract: In this work, 4*H*-pyran derivatives were synthesized via a green one-pot three-component reaction of aldehyde, malononitrile and a β-ketoester in the presence of copper ferrite magnetic nanoparticles at room temperature in ethanol via an environmentally friendly, simple and economical procedure.

Keywords: Nanocatalyst, Multicomponent reactions, 4*H*-Pyran, Copper ferrite, Magnetic.

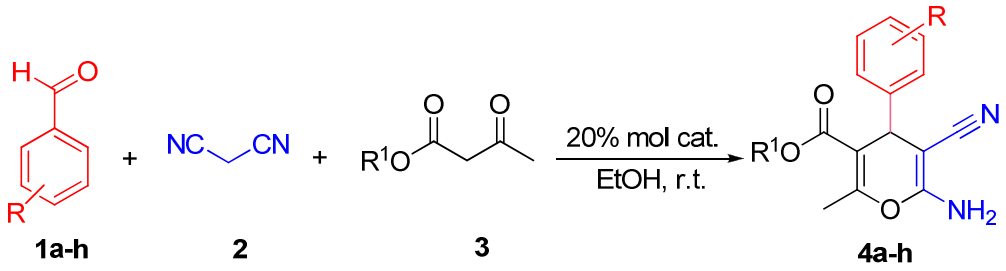
Introduction

4*H*-Pyran derivatives are an important class of heterocyclic compounds because of their biological and pharmaceutical activities [1]. They also constitute a structural unit of many natural products. These compounds include various biological activities like antitumor, antibacterial, antiviral, antiallergic, spasmolytic, diuretic, anti-coagulant and anti-anaphylactic [2,3]. In addition, these compounds are used in the treatment of Alzheimer, Schizophrenia, and Mycolonous diseases [4]. Previously, many methods were reported in the literature for the synthesis of 4*H*-pyrans including a two-step method containing cyclization of arylidene malononitriles with β-dicarbonyl compounds in the presence of catalysts such as MgO [3]. Most of these protocols suffer from long reaction times, difficulty of recovering the catalysts and the use of volatile solvents. Another route for synthesis of 4*H*-pyrans is one-pot three-component reaction of aryl aldehydes, malononitrile, and a β-dicarbonyl with various reaction conditions such as use of biocatalyst [2], nanocatalyst such as $SnCl_2$/nano SiO_2 [5] and use of organic base

such as piperidine [6] or infrared irradiation-assisted reaction [7]. These protocols suffer from one or more disadvantages too, such as high temperatures, long reaction times, low yields, and tedious workup procedures. Thus, the introduce of a new route for efficient synthesis of 4*H*-pyrans in mild conditions, short reaction times and ease of catalyst recycling is of prime importance.

Recently, environmental pollution and the economic crisis have become very important global challenges. As a result, industrial and manufacturing units including chemicals and pharmaceutical companies show propensity to environmentally friendly protocols that is so-called green and sustainable protocols. One of the important strategies in green chemistry is multicomponent reactions (MCRs). On the other hand, catalysts are powerful tools to improve reaction conditions. Application of nanoscience in this field leads to a wide range of academic and industrial researches to obtain green procedures [8].

Due to wide biological and pharmaceutical activities of 4*H*-pyrans, disadvantage of reported synthetic routes and in continuation of our interest in the application of new catalysts in organic synthesis via MCRs [9], herein, we represent an environmentally friendly synthesis of 4*H*-pyrans **4** via a green one-pot three-component reaction aldehyde **1**, malononitrile **2**, methylacetoacetate or ethylacetoacetate **3** using $CuFe_2O_4$ MNPs as an efficient catalyst under mild reaction conditions in good to excellent yields (Scheme 1).



Scheme 1. Synthesis of 4*H*-pyran derivatives.

Experimental

General

All solvents, chemicals and reagents were purchased from Merck, Fluka and Aldrich. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected.

Preparation of $CuFe_2O_4$ magnetic nanocatalyst

$CuFe_2O_4$ nanoparticles were prepared by co-precipitation of $Cu(NO_3)_2$ and $Fe(NO_3)_3$ in water in the presence of sodium hydroxide. Briefly, to a solution of $Fe(NO_3)_3.9H_2O$ (0.05 mol) and $Cu(NO_3)_2.3H_2O$ (0.025 mol) in 100 ml of distilled water, 75 ml of NaOH 4 M was added at room temperature over a period of 10 min to form reddish-black precipitate. Then the reaction mixture was warmed to 90 ºC and stirred. After 2 h, it was cooled to room temperature and the formed magnetic particles were separated by a magnetic separator. The catalyst was washed with water and kept in air oven over night at 80 ºC. Then the catalyst was ground in a mortar-pestle and kept in a furnace at 800 ºC at a heating rate of (2 ºC/min) and cooled to 100 ºC at (5 ºC/min) in air [10].

Synthesis of 4H-pyran derivatives (**4a-h**)

A solution of an aldehyde **1** (1 mmol), malononitrile **2** (1 mmol), methylacetoacetate or ethylacetoacetate **3** (1 mmol) and $CuFe_2O_4$ (20 mol%) was stirred in ethanol (5 mL) at room temperature. After completion of the reaction, as indicated by TLC, the catalyst was removed from reaction mixture by an external magnet and the product solidified at room temperature. The solid product was filtrated and then consequentially washed with ethanol, and dried in air.

Results and discussion

In this article, we have described a three-component reaction between aryl aldehydes, malononitrile, and a β-dicarbonyl compound in the presence a catalytic amount of MNPs at room temperature in ethanol. As it can be seen from Table 1, various aldehydes and β-ketoesters applied to reaction and 4*H*-pyrans **4a-h** were obtained in high yields. The catalyst was simply

separated by using an external magnet, and the pure products were obtained by crystallization from ethanol.

Table 1. Synthesis of 4*H*-pyran derivatives **4a-h**.

Product	R	R^1	Mp (°C)	
			Observed	Reported[ref.]
4a	H	Et	189-193	189-191 [5]
4b	3-NO_2	Et	187-188	187-188 [11]
4c	4-NO_2	Et	179-181	180-182 [5]
4d	2-Cl	Et	190-192	191-192 [4b]
4e	4-OMe	Et	133-136	134-136 [12]
4f	3-OH	Et	168-171	164-165 [3]
4g	3-NO_2	Me	210-212	212-213 [13]
4h	4-NO_2	Me	169-171	170-172 [14]

Conclusions

In summary, we have described a simple method for the synthesis of 4*H*-pyrans using $CuFe_2O_4$ nanoparticles as a reusable and efficient nanomagnetic catalyst. Short reaction times, green solvent, good to excellent yields, ease of catalyst recycling, simple work up procedure and mild conditions are the advantages of this protocol.

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