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One pot multi-component green synthesis of pyridine derivatives using malononitrile and efficient nanocatalyst

Mahboubeh Ghasemian Dazmiri[a*], Samaneh Vaseghi[b] and Maryam Kohi[c]

[a]*Department of Chemistry, Facualty of Chemistry, University of Mazandaran, Babolsar, Iran.*
[b]*Department of Chemistry, Science and Research Branch, Islamic Azad University, Tehran, Iran*
c Departmeny of Chemistry, Tarbiat Modares University, Tehran, Iran

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Abstract: In this research, the Fe_3O_4/ZnO magnetic nanoparticles were synthesized through a green method using *Petasites hybridus* rhizome water extract as a reducing and stabilizing agent. The morphology and size of the Fe_3O_4/ZnO MCNPs was identified utilizing XRD, SEM and EDX analysis. The catalytic activity of the Fe_3O_4/ZnO MCNPs was evaluated in the efficient and green synthetic method for preparation of pyran drivatives in excellent yield via four component condensations of aromatic aldehyde, malononitrile, hydrazine and dimethyl acetylenedicarboxylate in water as green solvent. The turn over frequency (TOF) values of the catalysts are higher than some of the previously reported catalysts.

Keywords: Malononitrile, pyridines, dimethyl acetylenedicarboxylate, Fe_3O_4/ZnO nanoparticles, Multi-component reaction.

Introduction

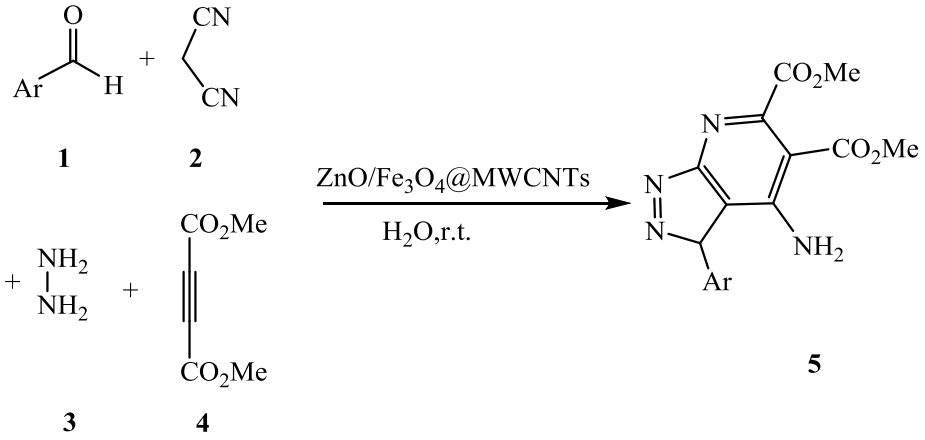
Multicomponent reactions (MCRs) are generally defined as reactions where more than two starting materials react to form a product. Generally, there are three different possible classification schemes of MCRs according to reaction mechanism, components involved, or intrinsic variability [1]. The development of new MCRs is an interesting research topic in applied areas of organic, medicinal, and pharmaceutical chemistry [2]. MCRs have attracted considerable interest owing to their exceptional synthetic efficiency. Hundreds of MCRs have recently been described. These reactions play a pivotal role in the synthesis of natural and unnatural products because of their importance of therapeutic and pharmacological uses [3–7]. *N*-Heterocycles receive considerable attention in the literature as a consequence of their exciting biological properties and their role as pharmacophores [8].

*Corresponding author. E-mail: pghm49@yahoo.com

Among a large variety of *N*-containing heterocyclic compounds, have received considerable attention because of their pharmacological properties and clinical applications [9-12]. Six-membered heterocyclic compounds containing oxygen such as pyrans constitute an important class of biologically active natural and synthetic products, playing a fundamental role in bioorganic chemistry and continue to attract interest.[13] In fact, pyrans and fused pyrans are biologically attractive compounds with antimicrobial [3], antibacterial [14], antifungal [15], antitumor [16], anticoagulant, diuretic, spasmolitic and antianaphylactic activities [17-19]. For the synthesis of some organic compounds, the nano catalyst compared to their bulk sized samples show good catalytic activity [20-21]. One green procedure for producing of nanoparticles is biosynthesis of nanoparticles using plants, bacteria, fungi and algae with biomedical applications. The classical method to synthesis of metal oxide nanoparticles using hazardous chemicals and has a negative effect for the environment. Green

synthesis of metal oxide nanocomposite has received special attention due to a cheaper and environmentally friendly method.It can refer to the formation of nanoparticle structures which capped by organic materials from living organisms or plants. [22-23] This method is a cheap, bio friendly, safe and green procedure [24]. These plants extract show some phytochemicals properties that play in both decreasing capping and stabilization agent. Recently, nanoparticles have become the subject of important research, since they have shown to be potential in many applications [25-27]. Commonly, several various chemical and physical methods have been applied so far for the preparation Fe_3O_4/ZnO MNPs. The Fe_3O_4 encapsulated with ZnO nanoparticles gives better results in biomedicine because ZnO is biocompatible (non-toxic) and easy to penetrate cells.[30] Gordon et al. in 2011[28] synthesized Fe_3O_4/ZnO MNPs and studied its antimicro-bial activity. Li et al. in 2016 [29] prepared Fe_3O_4/ZnO MNPs used as a nanoprobe for fluorescent chemosensor. Roeinfard et al. in 2017 synthesized Fe_3O_4/ZnO MNPs sol-gel method and investigated its cytotoxicity against breast cancer cells.Diverse physical and chemical methods are employed for the preparation of Fe_3O_4 and Fe_3O_4/ZnO MNPs such as co-precipitation, hydrothermal, microemulsion and biosynthesis [30-32]. Also, compounds that have the antioxidant activity due to their redox properties and chemical structure have chief roles such as middle metals chelators and filling singlet and triplet oxygen molecules with the negative effect of free radicals. Many diseases such as cardiovascular, inflammatory bowel syndrome, cancer, ageing, atherosclerosis, and Alzheimer's disease could be prevented or decreased by employing these compounds. At present, bacteria that are resistant to drugs have generated considerable problems in the performance of many communicable diseases. Therefore, discovering new ways to extirpate these pathogens are important. For this reason, recent studies have focused on the study of the antibacterial effects of new synthesized compounds. Due to importance of heterocyclic compounds [33-36] we try to expand new synthetic method for synthesis of these compounds.

Herein we report a convenient and facile one pot method for the synthesis of pyridine derivatives **5** in high yields via four-component reaction between aromatic aldehydes **1**, malononitrile **2,** hydrazine **3** and dimethyl acetylenedicarboxylate **4** in the present of Fe_3O_4/ZnO nanoparticles as in water at room temperature (Scheme **1**).



Scheme 1: Synthesis of pyridine derivatives

Results and discussion

In this research we investigate the synthesis of yridine derivatives **5** *via* four component reaction of aromatic aldehydes **1**, malononitrile **2,** hydrazine **3** and dimethyl acetylenedicarboxylate **4** in the presence of catalytic amount of Fe_3O_4/ZnO MCNPs in water at room temperature in good to excellent yield and low reaction time (Scheme 1, Table 2). The result of our optimization studies in catalyst charging are presented

in Table 1. As shown in Table 1, the reaction did not occur without any catalyst (Table 1, entry 1) and the yield of the preferred product was increased when bio Fe_3O_4/ZnO MCNPs was utilized (Table 1, entry 10). The yield increased effortlessly with catalyst fill up to 10% but further increase led to diminish of product exchange.

Table 1. Optimization the reaction condition for synthesis of **5a**.

Entry	Catalyst (10 mol%)	Temp. ^oC	Time (min)	Yeild (%)[a]
1	none	r.t.	180	----
2	CM-ZnO	r.t.	35	55
3	CM-ZnO	80	25	57
4	Bio-ZnO-NPs	r.t.	20	85
5	Bio-ZnO-NPs	80	10	85
6	Bio-Fe_3O_4-MNPs	r.t.	30	70
7	Bio-Fe_3O_4-MNPs	80	25	70
8	TiO_2-NPs	r.t.	40	58
9	CuO-NPs	r.t.	35	67
10	**Bio-Fe_3O_4/ZnO MNPs**	**r.t.**	**10**	**92**
11	Bio-Fe_3O_4/ZnO MNPs	80	10	90

Table 2. The diversity of pyridine derivatives

Entry	Ar	Time(min)	Yield[b] (%)
5a	4-NO_2-C_6H_4	35	92
5b	2-Cl-C_6H_4	40	86
5c	C_6H_5	40	90
5d	4-Cl-C_6H_4	40	95
5e	2-NO_2-C_6H_4	40	85
5f	4-Br-C_6H_4	40	90
5g	4-Me-C_6H_4	45	82
5h	2,4-Cl-C_6H_3	35	90
5i	3-CN-C_6H_4	35	87
5j	4-F-C_6H_3	35	90
5k	C_2H_5	50	-

Experimental

Apparatus and analysis

Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a

FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-500 Avance spectrometer at solution in DMSO-d_6 using TMS as internal standard. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

Preparation of Bio-Fe_3O_4/ZnO MNPs

Dried *Petasites hybridus* rhizome (10 g) was poured in 100 mL water in two-neck round bottom flask (250 mL) under reflux condition. After 2 h, the mixture was filtered and water extract was applied for preparation of Fe_3O_4/ZnO-MNPs as following. $Zn(OAC)_2$ (1.5 g) and $FeCl_2.4H_2O$ (1.5 g) was solved in deionized water (10 mL). Then, *Petasites hybridus* rhizome water extract (30 mL) was added to previous mixture gently at 85 ^oC in round bottom flask for 8h. Then it was cooled to room temperature, sonicated for 10 min and were centrifuged at 7000 rpm for about 10 min for removing the unwanted organic matters and then were filtered. The precipitate was collected by filtration and washed with distilled water and ethanol (96%) for several times. The samples were then heated at 500 °C for 1 h. Bio-Fe_3O_4/ZnO MCNPs was dried in the air at room temprature during 24 h.

Typical procedure for the synthesis of pyridine derivatives 4:

A mixture of malononitrile **1** (1.0 mmol), aromatic aldehyde **2** (1.0 mmol), hydrazine **3** (1.0 mmol), and dimethyyl acetylenedicarboxylate **4** (1.0 mmol) Fe_3O_4/ZnO MNPs (0.02 mmol) was mixed for 35-45 min. After completion of the reaction as indicated by TLC, the solid residue was dissolved in water to separate the catalyst and wash with diethylether. By recrystallization from ethanol, pure products were obtained.

Selected spectral data

7-amino-5-(4-chlorophenyl)-1,2,3,5-tetrahydro-1,3-dioxo-2-pyridine-6-carbonitrile 5a:

White powder mp >223 ºC, yield 95%, IR (KBr) (ν_{max}, cm^{-1}):1731, 1712 (CO ester), ^{1}H NMR (500 MH_Z, DMSO-d_6): δ = 6.03 (1H, s, CH), 7.35-8.35 (11H, m, *H*-Ar and NH_2). ^{13}C NMR (125.8 MH_Z, DMSO-d_6): δ = 61.7, 63.6, ,116.4, 124.2, 126.7, 128.4, 128.8, 129.2, 129.7, 130.3, 131.0, 131.8, 146.3, 148.0, 150. 7,154. Analyses: Calcd. for $C_{18}H_{12}ClN_5O_2$: C, 59.11; H, 3.31;N, 19.15 Found: C, 59.34; H, 3.12;N, 19.36 %.

Conclusion

In conclusion, we have investigated the reaction of malononitrile 1, aromatic aldehyde 2, hydrazine 3, and dimethyyl acetylenedicarboxylate 4 in water as green solvent at room temperature in the presence of catalytic amount of Fe3O4/ZnO-MCNPs which are produced pyran derivatives in excellent yields. The magnetically separable Fe3O4/ZnO-MCNPs were synthesized through a green method using Petasites hybridus rhizome water extract as a reducing and stabilizing agent. The morphology and size of the Fe3O4/ZnO-MCNPs was identified utilizing XRD, SEM and EDX analysis. The catalytic activity of the green synthesized Fe3O4/ZnO-MCNPs was evaluated in the efficient and green synthetic method for achieving of pyran derivatives in good to excellent yield. The present method carries the advantage that, not only is the reaction performed under neutral conditions, but also the substrates can be reacted without any prior activation or modification. The simplicity of the present procedure makes it an interesting alternative to complex multistep approaches.

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