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Fe₃O₄ nano-particles supported on cellulose as an efficient catalyst for the synthesis of pyrimido[4,5-*b*]quinolines in water

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Abstract Fe_3O_4 nano-particles supported on cellulose were provided as a catalyst via in situ preparation of Fe_3O_4 nano-particles and their deposition on cellulose. This catalyst, after characterization with TEM and FAAS analyses, was used as an efficient heterogeneous catalyst for the synthesis of pyrimido[4,5-*b*]quinolines. Three-component reaction of various aromatic aldehydes, 6-amino-1,3-dimethyluracil, and dimedone or 1,3-cyclohexadione in H₂O as a green solvent under reflux conditions after 2 h gave pyrimido[4,5-*b*]quinolines in high yields. Fe_3O_4 supported on cellulose was recycled in the reaction for 5 cycles without significant decrease in activity.

Keywords Fe_3O_4 nano-particles \cdot Cellulose \cdot Pyrimidine \cdot Quinoline \cdot Heterogeneous catalyst

Introduction

Today, most emphasis of chemical synthesis is on the development of green synthetic routes with heterogeneous catalysts and H_2O media [1]. Supported magnetic nanoparticles (NPs) are interesting heterogeneous catalysts with high surface area due to distribution of metal on the support [2]. They generally gave higher yield in low catalysts loading compared to conventional heterogeneous catalysts. Cellulose is the most important biopolymer which was used as a support. Cellulose is characterized by its hydrophilicity, chirality, biodegradability, and broad chemical

modifying capacity. These abilities of the cellulose make it an interesting support in catalytic reactions [3].

Quinolines are important heterocyclic compounds due to their various biological and pharmaceutical activities [4]. Some important drugs such as quinine, chloroquine, luotonine-A, and camptothecin have quinoline moiety [5]. Pyrimidine-containing organic compounds are of growing interest due to their biological potencies such as AbI kinase inhibitor, tyrosine phosphatase inhibitor, antiviral and calcium channel antagonist activities [6-8]. Some functionalized pyrimidines have also been identified as a new class of fibroblast growth factor receptor (FGFR3) tyrosine kinase inhibitors [9]. Recently, significant attempts were performed to the synthesis of pyrimido[4,5b]quinolines as a combination of pyrimidine and quinoline chemistry via multi-component reactions using various catalysts [10–18].

Herein, Fe₃O₄ NPs supported on cellulose (Fe₃O₄NPscell) was prepared as a heterogeneous recoverable catalyst and applied for the synthesis of pyrimido[4,5-*b*]quinolines **4a–4q** in H₂O under reflux conditions (Scheme 1).

Results and discussion

Fe₃O₄ NPs supported on cellulose were obtained with the alkalinization of a mixture containing cellulose, FeSO₄ and Fe₂(SO₄)₃ with ammonium hydroxide at 60 °C. Before addition of ammonium hydroxide, cellulose was stirred with FeSO₄ and Fe₂(SO₄)₃ for 1 day. Providing of these conditions allowed to the primary coordination of Fe ions to cellulose which led to the size controlling and uniform distribution of Fe₃O₄ NPs on the support. The results showed that the transformation of Fe(II) and Fe(III) into Fe₃O₄ after coordination to cellulose gave the homogenous smaller

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Scheme 1



 Fe_3O_4 NPs distributed on the surface and it would be able for us to make a good conversion with low loading of Fe_3O_4 .

Vacuum-dried Fe₃O₄NPs-cell was employed for the transmission electron microscopy (TEM) and flame atomic absorption spectroscopy (FAAS) analysis. The TEM images of the Fe₃O₄NPs-cell revealed that a large number of Fe₃O₄ NPs with the particles size between 11 and 24 nm were formed and uniformly distributed onto the surface of cellulose after deposition (Fig. 1). Fe₃O₄ loading in the Fe₃O₄NPs-cell was determined to be 4.72 wt%, based on FAAS analysis.

The catalytic activity of Fe₃O₄NPs-cell was evaluated for the synthesis of pyrimido[4,5-*b*]quinolines. For optimization of the reaction conditions, the reaction of benzaldehyde (**1a**), dimedone (**2**), and 6-amino-1,3-dimethyluracil (**3**) as a model reaction was investigated. As shown in the Table 1, it was found that 0.04 g of Fe₃O₄NPs-cell (0.9 mol% of Fe₃O₄) in H₂O under reflux conditions is the best reaction condition (entry 3). It is important to note that whilst organic solvents such as MeOH and EtOH gave similar yields (entries 5–7), H₂O was selected as the solvent due to its accordance with the green chemistry principle.

To evaluate the use of this interesting approach, a variety of aldehydes and cyclic 1,3-diketones 2 were examined which good library of pyrimido[4,5-*b*]quinolines 4 were

Yield/%^a Entry Temp./°C Catalyst amount/g Solvent 1 0.02 H_2O Reflux 47 2 0.03 H₂O Reflux 73 3 0.04 H₂O Reflux 89 4 0.05 H₂O Reflux 89 5 0.04 **EtOH** Reflux 89 6 0.04 CH₂Cl₂ Reflux 54 7 0.04 MeOH Reflux 89 8 0.04 CH₃CN Reflux 53 9 0.04 PhCH₃ Reflux 71 10 0.04 H_2O 25 39 77 11 0.04 H_2O 80 12 0.04 H_2O 90 82

Table 1 Effects of catalyst amount, solvent, and temperature on the

Reaction conditions: benzaldehyde (1a, 1.00 mmol), dimedone (2, 1.00 mmol), 6-amino-1,3-dimethyluracil (3, 1 mmol), 10 cm³ solvent, 2 h

^a Isolated yield

reaction yield

obtained in high yields (Table 2). The analyses of products **4a–4q** have good accordance with the reports [13–18].

Recyclability of the catalyst was examined too. For this reason, magnetically recovered Fe_3O_4NPs -cell from the reaction between benzaldehyde (1a), dimedone (2), and 6-amino-1,3-dimethyluracil (3) was washed with acetone (2 × 5 cm³), dried in the oven (60 °C, 2 h), and then used again. This procedure was carried out for five times (Table 3). It is clear that by successive use of the catalyst, no decrease in the reactivity can be seen for Fe₃O₄NPs-cell.

In conclusion, bio-supported Fe_3O_4 nano-particles as a catalyst were prepared by uniform distribution of Fe_3O_4 NPs (average particles size 11–24 nm) onto cellulose. This



Fig. 1 TEM images of Fe₃O₄NPs-cell sample

| Table 2 | Synthesis | of pyrimide | 5[4,5- <i>b</i>]qı | uinolines 4a–4q |
|---------|-----------|-------------|---------------------|-----------------|
|---------|-----------|-------------|---------------------|-----------------|

| Entry | Aldehyde 1 | R | Product | Yield/% ^a | Melting point/°C | |
|-------|--|----|------------|----------------------|------------------|--------------|
| | | | | | Found | Reported |
| 1 | C ₆ H ₅ | Me | 4 a | 89 | 267-270 | 268–270 [18] |
| 2 | $4-OHC_6H_4$ | Me | 4 b | 86 | >300 | >300 [15] |
| 3 | $3-NO_2C_6H_4$ | Me | 4c | 87 | 220-222 | 220–223 [16] |
| 4 | $4-NO_2C_6H_5$ | Me | 4d | 96 | 221-224 | 222-224 [18] |
| 5 | 3-BrC ₆ H ₄ | Me | 4e | 92 | 280-283 | 280–282 [16] |
| 6 | $4-ClC_6H_4$ | Me | 4 f | 91 | 289–292 | 289–292 [14] |
| 7 | 2-ClC ₆ H ₄ | Me | 4 g | 88 | >300 | >300 [14] |
| 8 | 4-OCH ₃ C ₆ H ₄ | Me | 4h | 87 | >300 | >300 [14] |
| 9 | $4-BrC_6H_4$ | Me | 4i | 91 | 281-283 | 280-282 [14] |
| 10 | 2-Thienyl | Н | 4j | 87 | 293-296 | 295–297 [15] |
| 11 | $4-BrC_6H_4$ | Н | 4 k | 86 | 281-283 | 281–283 [15] |
| 12 | $4-NO_2C_6H_4$ | Н | 4 m | 95 | 301-303 | 301-303 [13] |
| 13 | $4-FC_6H_4$ | Н | 4n | 89 | 310-313 | 311–313 [13] |
| 14 | $4-ClC_6H_4$ | Н | 40 | 90 | 310-313 | 310–313 [17] |
| 15 | $4-CH_3C_6H_4$ | Н | 4q | 92 | 274–276 | 274–276 [13] |

Reaction conditions: aldehyde 1 (1.00 mmol), 2,4-diketone 2 (1.00 mmol), 6-amino-1,3-dimethyluracil (3, 1 mmol), 0.04 g Fe₃O₄NPs-cell, 10 cm³ H₂O, reflux, 2 h

^a Isolated yield

Table 3 Recycle of the catalyst

| Cycle | Fe ₃ O ₄ -cell/g | Yield/% | |
|-------|--|---------|--|
| 1 | 0.040 | 95 | |
| 2 | 0.039 | 95 | |
| 3 | 0.038 | 94 | |
| 4 | 0.038 | 93 | |
| 5 | 0.038 | 93 | |
| | | | |

Reaction conditions: benzaldehyde (**1a**, 1.00 mmol), dimedone (**2**, 1.00 mmol), 6-amino-1,3-dimethyluracil (**3**, 1 mmol), 5 cm³ H₂O, reflux, 2 h

^a Isolated yield

catalyst was successfully examined in the synthesis of pyrimido[4,5-*b*]quinolines via three-component reaction in H_2O as the solvent under reflux conditions with fairly high yields. This method has some advantages including low catalyst amounts of Fe₃O₄, heterogeneous recyclable catalyst with natural base and H_2O as the solvent. The work-up procedure is very simple, and the products do not require further purification. The simplicity of the present route and environmental-friendly reaction conditions make it an interesting alternative to other approaches.

Experimental

The chemicals used in this work were purchased from Merck and Fluka chemical companies. Melting points were measured on an Electrothermal 9100 apparatus. ¹H NMR spectra were recorded on a Bruker WP 200 SY spectrometer 250.13 MHz in DMSO- d_6 solution with TMS as internal standard. The ¹³C NMR spectra were recorded at 62.47 MHz; chemical shifts (δ scale) are reported in parts per million (ppm). Transmission electron microscopy and flame atomic absorption spectroscopy were performed by LEO 912AB electron microscope and Shimadzu model AA-680 atomic absorption spectrometer, respectively.

Preparation of Fe₃O₄NPs-cell

Cellulose (5.0 g) was added to a solution containing 0.1 g $FeSO_4$ ·7H₂O, 0.2 g $Fe_2(SO_4)_3$ and 30 cm³ H₂O and stirred for 1 day. After that, pH was adjusted to 10 with addition of ammonium hydroxide (25 %) and the reaction mixture was stirred for 1 h at 60 °C. The precipitated nano-catalyst was separated magnetically, washed with water until the pH reached 7, and then dried under a vacuum at 60 °C for 2 h.

Representative procedure: 1,3,8,8-tetramethyl-5phenyl-5,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,7H)-trione (4a)

To a magnetically stirred solution of 0.11 g benzaldehyde (1.00 mmol), 0.07 g dimedone (1.00 mmol), and 0.16 g 6-amino-1,3-dimethyluracil (**3**, 1.00 mmol) in 10 cm³ H₂O, 0.04 g Fe₃O₄NPs-cell was added and the reaction mixture was refluxed for 2 h. Upon completion (monitored

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