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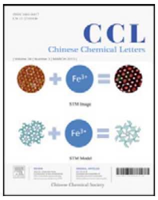

Original article

# Nano-$Fe_3O_4$ encapsulated-silica particles bearing sulfonic acid groups as a magnetically separable catalyst for green and efficient synthesis of functionalized pyrimido[4,5-*b*]quinolines and indeno fused pyrido[2,3-*d*]pyrimidines in water

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ABSTRACT

The magnetic nanoparticles supported silica sulfuric acid was used as an efficient catalyst for the synthesis of pyrimido[4,5-*b*]quinolines and indeno fused pyrido[2,3-*d*]pyrimidines in water. The desired products were obtained in excellent yields. $Fe_3O_4$@$SiO_2$–$SO_3H$ was readily recovered using an external magnet and could be reused several times without significant loss of reactivity.

## 1. Introduction

Multi-component coupling reactions (MCRs) have proved a highly valuable synthetic tool for building diverse and complex molecular structures through C–C and C-heteroatom bond formation. These types of reactions are especially attractive because of their atom economy, operational simplicity, reduction in the number of workup, extraction and purification processes and hence minimize waste generation. Recently this strategy has been used effectively in the synthesis of many biologically active substrates and natural products [1]. The usefulness of multi-component reactions is significantly expanded if they are conducted with green procedures.

Quinolines are valuable heterocyclic compounds due to their various biological and pharmaceutical activities [2]. These compounds have shown wide applications as key structural motifs in a large number of bioactive drugs such as Quinine, Chloroquine, Luotonine-A and Camptothecin [3]. Organic compounds containing pyrimidine scaffolds are of growing interest due to their biological potencies such as AbI kinase inhibitor [4], tyrosine phosphatase inhibitor [5], antiviral and calcium channel antagonist activities [6]. Moreover, appropriately functionalized pyrido[2,3-*d*]pyrimidines have also been identified as a new class of fibroblast growth factor receptor (FGFR3) tyrosine kinase inhibitors [7].

Supported magnetic metal nanoparticles have emerged as a new class of nano catalysts [8]. Because of their high surface area, they generally exhibit higher catalytic activity than conventional heterogeneous acid catalysts. Recently, sulfonic acid-functionalized silica-coated nano-$Fe_3O_4$ particles ($Fe_3O_4$@$SiO_2$–$SO_3H$) have been prepared in our laboratory as an efficient acid catalyst. It could be readily separated from the media using a simple external magnet and reused several times [9]. The process is more effective than filtration and centrifugation in preventing loss of the solid catalyst.

## 2. Experimental

*General procedure for the synthesis compounds* **6** *and* **8**: A mixture of 6-amino-1,3-dimethyl uracil (1.0 mmol), benzaldehyde (1.0 mmol), 1,3-diketone (1.0 mmol) and $Fe_3O_4$@$SiO_2$–$SO_3H$ (0.02 g) in distilled $H_2O$ (1 mL) was stirred for appropriate time at 70 °C. Upon completion of the reaction (monitored by TLC), the reaction mixture was allowed to cool to room temperature. The catalyst was separated from the solid crude product using an external magnet. The obtained solid was then filtered and the crude product collected and crystallized from EtOH to afford the pure product in 81%–95% yields.

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Data For **6c**: IR (KBr, cm$^{-1}$): $\upsilon_{max}$ 3410, 1666, 1612; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.26 (s, 3H), 1.28 (s, 3H), 2.26 (d, 1H, $J$ = 16.4 Hz), 2.31 (d, 1H, $J$ = 16.8 Hz), 2.44 (d, 1H, $J$ = 16.4 Hz), 2.50 (d, 1H, $J$ = 16.8 Hz), 3.29 (s, 3H), 3.59 (s, 3H), 5.12 (s, 1H), 7.44–7.11 (m, 4H), 9.12 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 18.4, 27.2, 27.3, 28.8, 29.2, 32.6, 32.8, 41.6, 50.2, 122.6, 123.3, 125.2, 126.3, 127.4, 129.65, 129.69, 130.5, 161.0, 203.2. Anal. Calcd. for $C_{21}H_{22}N_3O_3Br$: C 58.07, H 5.08, 9.68 N; found: C 57.99, H 5.01, N 9.75.

**6e**: IR (KBr, cm$^{-1}$): $\upsilon_{max}$ 3409, 1697, 1596; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.14 (s, 3H), 1.27 (s, 3H), 2.21 (d, 1H, $J$ = 16.4 Hz), 2.34 (d, 1H, $J$ = 16.8 Hz), 2.56 (d, 1H, $J$ = 16.4 Hz), 3.3 (s, 3H), 3.55 (s, 3H), 5.65 (s, 1H), 7.43–7.50 (m, 4H), 8.052 (s, 1 H), 12.62 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 18.4, 27.2, 27.3, 28.8, 29.2, 32.1, 32.6, 42.5, 51.0, 121.6, 124.7, 125.2, 126.3, 127.4, 129.65, 129.69, 135.4, 161.1, 203.0. Anal. Calcd. for $C_{21}H_{22}N_4O_5$: C 61.46, H 5.36, N 13.65; found: C 61.55, H 5.29, N 13.74.

**6j**: IR (KBr, cm$^{-1}$): $\nu_{max}$ 3402, 1697; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.33 (s, 3H), 3.34 (s, 6H), 3.52 (s, 6H), 5.64 (s, 1H), 7.06 (d, 2H, $J$ = 8.0 Hz), 7.12 (d, 2H, $J$ = 8.0 Hz), 14.54 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 28.7, 28.8, 29.6, 128.7, 129.9, 134.3, 135.0, 135.6, 150.4, 151.1, 159.5, 160.5. Anal. Calcd. for $C_{20}H_{22}N_4O_5$: C 60.30, H 5.52, N 14.07; found: C 60.21, H 5.45, N 14.15.

**8a:** IR (KBr, cm$^{-1}$): $\nu_{max}$ 1720, 1666, 1566, 1496; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 3.37 (s, 3H), 3.94 (s, 3H), 7.41–7.52 (m, 3H), 7.56 (d, 2H, $J$ = 7.4 Hz), 7.66–7.84 (m, 2H), 8.47–8.52 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 30.1, 37.5, 113.0, 118.6, 119.5, 125.7, 128.0, 128.1, 129.8, 130.3, 131.6, 132.5, 151.7, 158.4, 160.3, 170.2, 172.5, 185.5. Anal. Calcd. for $C_{20}H_{22}N_4O_5$: C 71.54, H 4.06, N 11.38; found: C 71.46, H 3.95, N 11.26.

## 3. Results and discussion

In continuation of effort to employ environmentally benign reaction media [10], we have attempted to develop catalytic application of $Fe_3O_4@SiO_2–SO_3H$ for clean synthesis of structurally diverse functionalized pyrimido[4,5-*b*]quinolines and indeno fused pyrido[2,3-*d*]pyrimidines *via* one-pot condensation of 6-amino-1,3-dimethyl uracil, 1,3-dicarbonyl compounds and aromatic aldehydes in water (Scheme 1).

**Table 1**

Optimization of reaction condition and comparison of the efficiency of $Fe_3O_4@SiO_2–SO_3H$ with other catalyst for the synthesis of 8,9-dihydro-1,3,8,8-tetramethyl-5-(4-chlorophenyl)pyrimido[4,5-*b*]quinoline- 2,4,6(1*H*,3*H*,5*H*,7*H*,10*H*)-trione (**6g**).

| Entry | Catalyst | Catalyst loading | condition | Time (min) | Yield (%) |
|---|---|---|---|---|---|
| 1 | *p*-TsOH | 20 mol% | $H_2O$/90 °C | 150 | 89 [11] |
| 2 | $InCl_3$ | 20 mol% | $H_2O$/reflux | 60 | 91 [12] |
| 3 | [bmim]Br[a] | 2 mL | 95 °C | 210 | 90 [13] |
| 4 | $Fe_3O_4@SiO_2–SO_3H$ | 20 mg | $H_2O$/70 °C | 25 | 92 |
| 5 | $Fe_3O_4@SiO_2–SO_3H$ | 20 mg | EtOH/reflux | 100 | 86 |
| 6 | $Fe_3O_4@SiO_2–SO_3H$ | 20 mg | $CH_3CN$/reflux | 100 | 51 |
| 7 | Nano-$Fe_3O_4$ | 20 mg | $H_2O$/70 °C | 25 | 70 |
| 8 | $Fe_3O_4@SiO_2$ | 20 mg | $H_2O$/70 °C | 25 | 49 |

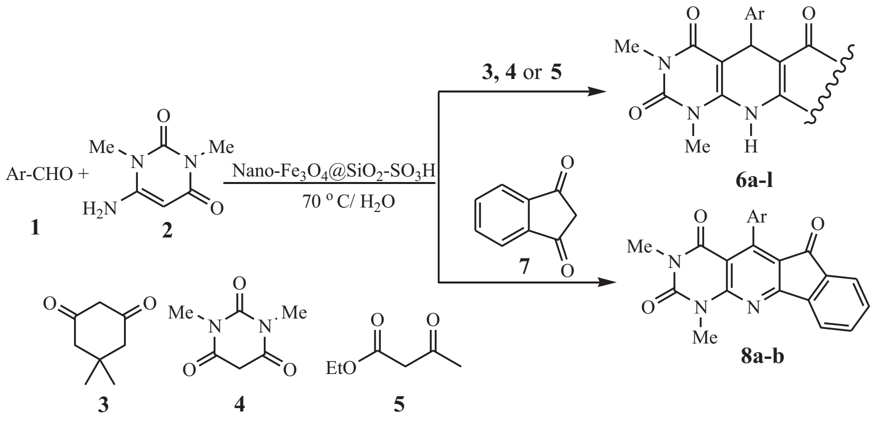
[a] 1-*n*-Buthyl-3-methylimidazolium bromide.

The efficiency of $Fe_3O_4@SiO_2–SO_3H$ as a catalyst for the synthesis of the model compound 8,9-dihydro-1,3,8,8-tetramethyl-5-(4-chlorophenyl)pyrimido[4,5-*b*]quinoline-2,4,6(1*H*,3*H*, 5*H*,7*H*,10*H*)-trione (**6g**) was compared with that of other catalysts reported in the literature (Table 1). It is clear from this Table that $Fe_3O_4@SiO_2–SO_3H$ has proved to be the more efficient catalyst for the synthesis of quinolines. The model reaction was performed using nano-$Fe_3O_4$ and $Fe_3O_4@SiO_2$ (Table 1, entries 7 and 8). As shown in Table 1, the $Fe_3O_4@SiO_2–SO_3H$ can act as a suitable catalyst in terms of yields. The proficient catalytic activity of $Fe_3O_4@SiO_2–SO_3H$ was related to the $–SO_3H$ groups of the catalyst, which could provide efficient acidic sites. Various solvents were also screened to test the efficiency of the catalyst in different reaction media (Table 1, entries 4–6). Product yields were found to be improved in water. It is noteworthy to mention that quantity of the catalyst plays an essential role in the formation of the desired product. The best result was obtained by using 0.02 g catalyst at 70 °C in aqueous medium (Table 1, entry 4). The starting materials were completely consumed. Furthermore, the easy recovery of the catalyst and simple workup in water follow principles of "green chemistry".

The advantages and limitations of this methodology were investigated by reacting 6-amino-1,3-dimethyl uracil and dimedone with various substituent benzaldehydes to give functionalized pyrimido[4,5-*b*]quinolines (Table 2, entries 1–9). Irrespective of the presence of an electron withdrawing or releasing substituent, the reaction proceeded fairly well and afforded the desired products in good yields. Similarly, scope of the reaction was also extended by reacting other 1,3-diketones such as 1,3-indanedione, 1,3-dimethylbarbituric acid and ethyl acetoacetate (Table 2, entries 10–14). As the results in Table 2 appended, $Fe_3O_4@SiO_2–SO_3H$ proved to be a useful nanomagnetic heterogeneous acid catalyst for green synthesis of functionalized pyrimido[4,5-*b*] quinolines and indeno fused pyrido[2,3-*d*]pyrimidines in excellent yields.

The possible mechanism is postulated in Scheme 2. The Knoevenagel condensation and Michael addition produce intermediates A and B respectively. Subsequently, annulation, dehydration and aromatization on intermediate B yield the final product.

$Fe_3O_4@SiO_2–SO_3H$ was simply recovered with an external magnet, washed with chloroform several times and dried at 60 °C for 1 h. The recovered catalyst successfully catalyzed synthesis of **6g** three consecutive times without a significant drop in product



**Scheme 1.** Synthesis of pyrimido[4,5-*b*]quinolines and indeno fused pyrido[2,3-*d*]pyrimidines.

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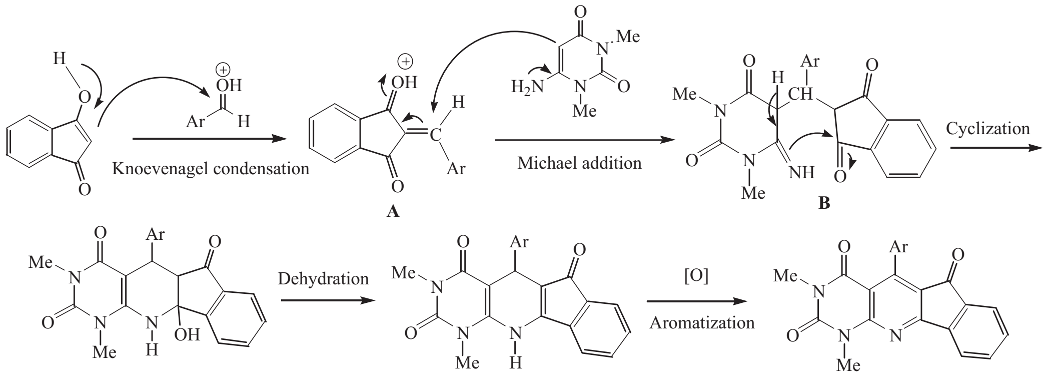
**Table 2**
Synthesis of pyrimido[4,5-*b*]quinolines and indeno fused pyrido[2,3-*d*]pyrimidines using $Fe_3O_4$@$SiO_2$–$SO_3H$ in water.

| Entry | Ar-CHO | Diketone | Product | Time (min) | Yield (%) | Mp (Lit.)°C |
|---|---|---|---|---|---|---|
| 1 | $C_6H_5$ | Dimedone | **6a** | 30 | 92 | 268–270(268)[14] |
| 2 | 4-OMe-$C_6H_4$ | Dimedone | **6b** | 40 | 86 | >300 (>300)[13] |
| 3 | 3-Br-$C_6H_4$ | Dimedone | **6c** | 35 | 90 | 280–282 |
| 4 | 4-$NO_2$-$C_6H_4$ | Dimedone | **6d** | 25 | 92 | 223–225(222–224)[12] |
| 5 | 3-$NO_2$-$C_6H_4$ | Dimedone | **6e** | 30 | 90 | 220–223 |
| 6 | 2-Cl-$C_6H_4$ | Dimedone | **6f** | 35 | 81 | >300 (>300)[13] |
| 7 | 4-Cl-$C_6H_4$ | Dimedone | **6g** | 25 | 92 | 289–292(291)[14] |
| 8 | 4-F-$C_6H_4$ | Dimedone | **6h** | 30 | 89 | 234–236 |
| 9 | 2-Thiophen | Dimedone | **6i** | 35 | 87 | 295–297(296–298)[12] |
| 10 | 4-Me-$C_6H_4$ | Dimethylbarbituric acid | **6j** | 20 | 95 | 238–240 |
| 11 | $C_6H_5$ | Ethyl acetoacetate | **6k** | 30 | 92 | 298–299 |
| 12 | 4-OMe-$C_6H_4$ | Ethyl acetoacetate | **6l** | 35 | 87 | 267–269 |
| 13 | $C_6H_5$ | 1,3-Indanedione | **8a** | 30 | 90 | >300 |
| 14 | 4-$NO_2$-$C_6H_4$ | 1,3-Indanedione | **8b** | 25 | 94 | 258–260(252–254)[12] |



**Scheme 2.** Plausible mechanism.

yields. The yields for the three runs were found to be 92%, 88% and 81%, respectively.

## 4. Conclusion

In conclusion, we have developed an efficient and eco-friendly method for one pot synthesis of pyrimido[4,5-*b*]quinolines and indeno fused pyrido[2,3-*d*]pyrimidines using nano-$Fe_3O_4$@$SiO_2$–$SO_3H$ as the catalyst in water under mild conditions. The catalyst is completely magnetically recoverable and the efficiency of the catalyst remains unaltered after three cycles. These advantages make this methodology attractive for large-scale synthesis.

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