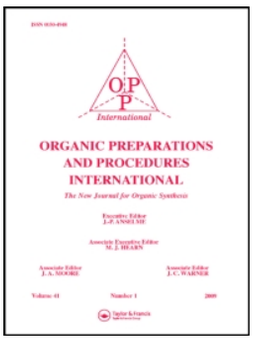

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OPPI BRIEF

One-Pot Synthesis of Polyhydroquinolines Catalyzed by $ZnCl_2$ Supported on Nano Fe_3O_4@SiO_2

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The development of an atom-economical approach for the efficient construction of diversely functionalized molecules from easily accessible starting materials is always a special issue for synthetic organic chemists.[1–3] The 4-substituted 1,4-dihydropyridine (1,4-DHP) nucleus is a rich source of biological molecules which are useful as antihypertensive, vasodilator, antitherosclerotic, antitumor, geroprotective and antidiabetic agents.[4–8] These compounds also have activities as neuroprotectants and as platelet anti-aggregants. They have cerebral antischaemic activity in the treatment of Alzheimer's disease and chemosensitizer behavior in tumor therapy.[9] The valuable cardiovascular agents nifepidin, felodipine and amlodipine belong to this category of compounds, and they play important roles in hypertension treatments.[10] They have shown usefulness in the treatment of angina pectoris and other cardiovascular diseases.[11–12]

The best methods for the synthesis of polyhydroquinolines are multicomponent reactions. These advantageous reactions are in agreement with green chemistry principles such as atom economy and resource-effectiveness bond-forming efficiency.[13–17]

There are many approaches in the literature for the preparation of polyhydroquinolines. They include the use of such catalysts as Co_3O_4-CNTs,[18] $Ni_{0.35}Cu_{0.25}Zn_{0.4}Fe_2O_4$ MNPs,[19] ceric ammonium nitrate,[20] cetyltrimethylammonium bromide,[21] MCM-41,[22] *p*-TSA,[23] scolecite,[24] hafnium(IV)bis(perfluorooctanesulfonyl)imide,[25] PPA-SiO_2,[26] TiO_2 NPs,[27] $Al_2(SO_4)_3$,[28] VDDAP,[29] Fe_3O_4@chitosan,[30] Fe_3O_4-SA-PPCA,[31] $SbCl_3$-SiO_2,[32] MoO_3-SiO_2,[33] 1,3-di-(bromo or chloro)-5,5-dimethylhydantoin[34] and the polymeric catalyst [poly(AMPS-co-AA)].[35]

In spite of the undeniable utility of the above methods, the majority have some limitations including low yields, long reaction times, difficult preparations of the catalysts or the use of hazardous solvents. In order to overcome these limitations and in

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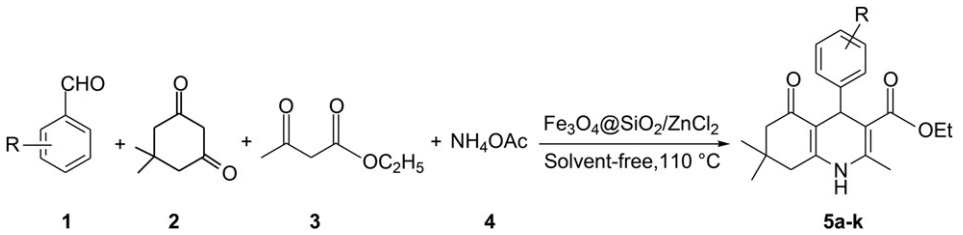


Scheme 1. Synthesis of polyhydroquinolines using Fe_3O_4@SiO_2/$ZnCl_2$ as a catalyst under solvent-free conditions.

continuation of our research on heterocyclic synthesis,[36–46] we became interested in using a nanomagnetic catalyst for the synthesis of polyhydroquinolines.

Nanocatalysts are remarkably efficient due to their incomparable properties, such as their large surface-to volume ratios, which dramatically increase their activity. This is conducive to high selectivity and stability. The principal methods for their separation are centrifugation and filtration which do have some limitations, including most significantly the loss of catalyst.[47–48] The best solution to overcome this particular limitation is to use magnetic nanoparticles. These can be easily separated just by using an external magnet.[49–53]

Because of its high surface area, excellent thermal and chemical stability and good accessibility,[54–55] silica has an excellent record as a support. Recently, magnetic silica nanoparticles have attracted great attention, because of their chemical inertness, excellent thermal stability and lack of toxicity. This allows nanoparticles to be used in organic reactions as catalysts or as supported catalysts.[56–67]

In the present research, we were interested in using a nanocatalyst which would incorporate $ZnCl_2$. The powerful Lewis acid properties of $ZnCl_2$ make it useful for organic reactions, and it has the advantages of low cost, nontoxicity and easy access.[68]

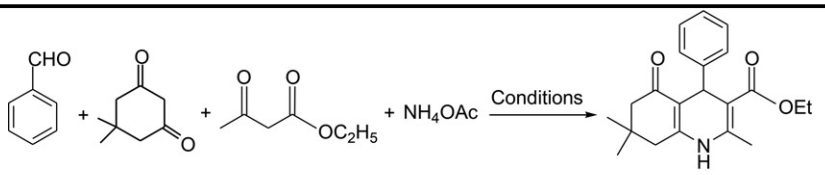
Thus, in our work, $ZnCl_2$ was immobilized on the surface of Fe_3O_4@SiO_2 core–shell nanoparticles[69] and was used in the synthesis of polyhydroquinoline derivatives (*Scheme 1*). This nanocatalyst can be easy separated from the reaction mixture and so it obeys one of the most important green chemistry principles, namely the recycling capability of the catalyst.

In order to obtain the best conditions for this reaction, we optimized temperature, solvent, and amount of catalyst and compared these to running the reaction in the absence of catalyst. Our study started by using benzaldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1.2 mmol), ammonium acetate (5 mmol) and Fe_3O_4@SiO_2/$ZnCl_2$ as catalyst. As shown in *Table 1*, the best result was achieved with 0.04 g of catalyst under solvent-free conditions at 110°C (*Table 1*, entry 1). Then we did the reaction with different amounts of catalyst and we found that 0.05 g is the optimum amount (*Table 1*, entry 7). We studied the reaction in the presence of Fe_3O_4 and $ZnCl_2$ separately, but the results were not satisfactory (*Table 1*, entries 8, 9). We did the reaction in the absence of catalyst, and again the results were not acceptable (*Table 1*, entry 10). Thus, we found that the best conditions for this reaction were 110°C and 0.05 g of Fe_3O_4@SiO_2/$ZnCl_2$ (entry 7).

In order to expand the scope of the reaction we used different aldehydes and studied the effect of electron-donating and electron withdrawing substituent groups on the reaction. The results are listed in *Table 2*. The average yield was 87%. Yields were uniformly high, and the process does not appear to be especially sensitive to the electronic nature of the groups.

In order to determine the recyclability of this nanocatalyst, we used it in the model reaction among benzaldehyde, ethyl acetoacetate, ammonium acetate and dimedone. After

Table 1
Optimization of Reaction Conditions



1 2 3 4 5a

Entry	Catalyst (g)	Conditions	Time (min)	Yield[a] (%)
1	Fe_3O_4@SiO_2/$ZnCl_2$ (0.04 g)	Solvent-free/110°C	25	88
2	Fe_3O_4@SiO_2/$ZnCl_2$ (0.04 g)	Solvent-free/100°C	25	82
3	Fe_3O_4@SiO_2/$ZnCl_2$ (0.04 g)	Solvent-free/120°C	25	89
4	Fe_3O_4@SiO_2/$ZnCl_2$ (0.04 g)	Ethanol/reflux	25	74
5	Fe_3O_4@SiO_2/$ZnCl_2$ (0.04 g)	Methanol/reflux	25	70
6	Fe_3O_4@SiO_2/$ZnCl_2$ (0.03 g)	Solvent-free/110°C	25	81
7	Fe_3O_4@SiO_2/$ZnCl_2$ (0.05 g)	Solvent-free/110°C	25	90
8	Fe_3O_4 (0.04 g)	Solvent-free/110°C	60	34
9	$ZnCl_2$ (0.04 g)	Solvent-free/110°C	25	72
10	–[b]	Solvent-free/110°C	60	28

[a]Isolated yield.
[b]This reaction was carried out in the absence of Fe_3O_4@SiO_2/$ZnCl_2$.

completion of the reaction (as determined by TLC, see Experimental Section), we added 2 ml of hot ethanol, stirred for 2 minutes, the Fe_3O_4@SiO_2/$ZnCl_2$ was separated using an external magnet and then dried at 100°C for 2 h. It was then reused in the same reaction for four successive runs in yields of 90%, 88%, 84% and 80% respectively.

In summary, we studied the synthesis of polyhydroquinoline derivatives using Fe_3O_4@SiO_2/$ZnCl_2$ as a nanocatalyst. This catalyst is excellent for this synthesis, giving pure products in high yields and short reaction times. An important aspect is the recyclability of this nanocatalyst, showing its economical and green qualities. We hope that our work will stimulate further applications of this catalyst.

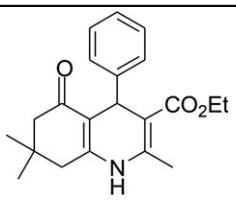
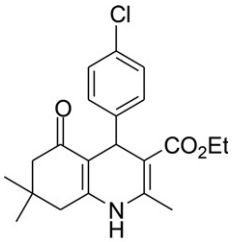
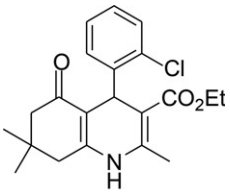
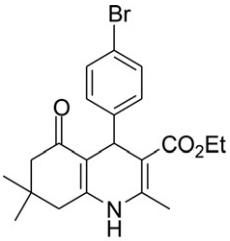
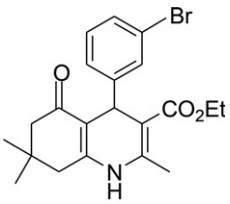
Experimental Section

All reagents were obtained from commercial sources. The measurements of melting points were done on a Stuart BI Branstead Electrothermal IA9200 apparatus and were uncorrected. A Shimadzu 435-U- 04 spectrophotometer (KBr) was used for recording the FT-IR spectra. ^{1}H NMR spectra were obtained using a Bruker 300 MHz spectrometer, in DMSO-d_6 or $CDCl_3$ and using TMS as the internal reference. The catalyst was prepared according to the method previously described.[69]

Genaral Procedure for Synthesis of Polyhydroquinolines using $ZnCl_2$ Supported on Fe_3O_4@SiO_2 Core–Shell Nanocatalyst

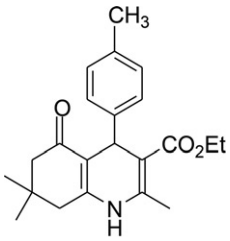
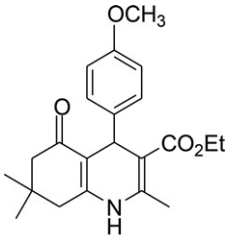
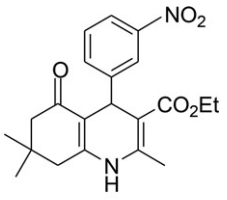
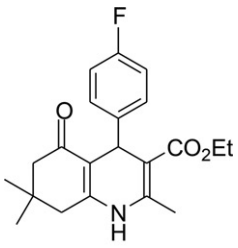
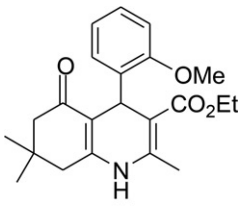
A mixture of aldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1.2 mmol), ammonium acetate (5 mmol) and Fe_3O_4@SiO_2/$ZnCl_2$ (0.05 g) was prepared. The

Table 2
One-Pot Synthesis of Polyhydroquinolines using Fe_3O_4@SiO_2/$ZnCl_2$

Entry	Product	Yield[a] (%)	Time (min)	mp (^{0}C) Found	mp (^{0}C) Lit.
1	 **(5a)**	90	25	204-206	203-204[18]
2	 **(5b)**	92	30	242-244	244-246[18]
3	 **(5c)**	78	35	208-210	210-211[18]
4	 **(5d)**	90	30	251-252	252-254[26]
5	 **(5e)**	90	30	232-234	231-234[19]

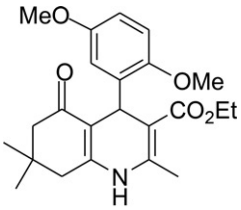
(*Continued*)

Table 2
(*Continued*)

6	 **(5f)**	90	40	258-260	260-263[26]
7	 **(5g)**	81	25	253-255	255-258[26]
8	 **(5h)**	93	30	178-179	178-180[23]
9	 **(5i)**	79	35	184-186	184-186[26]
10	 **(5j)**	81	35	193-195	192-193[34]

(*Continued*)

Table 2
(*Continued*)

11	 **(5k)**	92	25	160-162	158-160[28]

mixture was heated on an oil bath at 110°C for the appropriate time (*see Table 2*). The reaction progress was monitored by TLC (*n*-hexane:ethyl acetate, 2:1). After completion of the reaction (as determined by TLC) we added 2 ml hot ethanol to the reaction mixture and it was stirred for 2 minutes, then the Fe_3O_4@SiO_2/$ZnCl_2$ was separated using an external magnet and then dried at 110°C for 2 h. The resulting mixture was poured into crushed ice, and the final product was obtained through filtration and pure product was obtained by recrystallization from 96% ethanol.

Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(phenyl)5-(6H)-oxoquinoline-3-carboxylate (5a)

IR (KBr, disc) cm^{-1}: 3300, 3200, 3100, 2980, 1700, 1620, 1490, 1390, 1300, 1200, 710; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.85 (s, 3H), 1.01 (s, 3H), 1.14 (t, 3H), 2.06 (dd, 1H), 2.13 (dd, 1H), 2.28 (s, 2H), 3.18 (s, 3H), 3.98 (q, 2H), 4.91 (s, 1H), 6.90–7.22 (m, 5H_{arom}), 9.05 (s, 1H, NH, exchangeable with D_2O); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 194.54, 166.82, 149.10, 147.12, 144.24, 127.21, 127.03, 125.06, 110.28; 104.09, 58.71, 50.18, 35.72, 31.77, 28.90, 26.32, 18.09, 13.67.

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