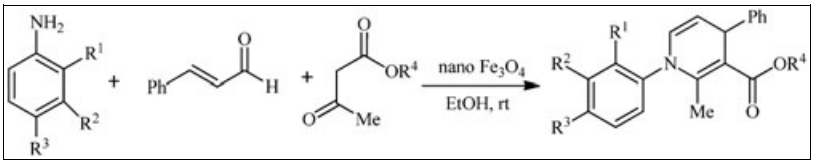
An Efficient One-Pot Synthesis of 1,4-Dihydropyridines Catalyzed by Magnetic Nanocrystalline Fe_3O_4

Shu-Hong Yang, Fei-Yang Zhao, Hong-Yan Lü, Jia Deng, and Zhan-Hui Zhang*

Key Laboratory of Inorganic Nanomaterial of Hebei Province, The College of Chemistry and Material Science, Hebei Normal University, Shijiazhuang 050016, China
*E-mail: Zhanhui@126.com

Received January 25, 2011
DOI 10.1002/jhet.953
Published online 29 October 2012 in Wiley Online Library (wileyonlinelibrary.com).



An efficient approach for one-pot three-component reaction of aromatic amines, α,β-unsaturated aldehydes and β-keto esters using magnetic nanocrystalline Fe_3O_4 as a catalyst has been described. The corresponding 1,4-dihydropyridines are obtained in good yields under mild conditions. In addition, the catalyst can be recovered with a magnet and reused at least five consecutive cycles without appreciable loss of its catalytic activity.

J. Heterocyclic Chem., **49**, 1126 (2012).

INTRODUCTION

Multicomponent, one-pot reactions represent a highly valuable synthetic tool for the construction of novel and complex molecular structures with a minimum number of synthetic steps [1–5]. 1,4-Dihydropyridines (1,4-DHPs) and their derivatives are important compounds not only in organic synthesis but also in medicinal chemistry. They were found to exhibit a variety of pharmacological and biological properties such as antitrypanosomal, anticancer, antibacterial, antitubercular, antitubercular, antileishmanial and antitrypanosomal, antihyperglycemic, antidyslipidemic, antiatherosclerotic, antioxidant, hepatoprotective, antimutagenic, antidiabetic, geroprotective, and photosensitizing activities [6–11] and HIV protease inhibition [12]. They are well known as the most important calcium channel modulators [13] and have emerged as one of the most important classes of drug for the treatment of hypertension [14]. Therefore, significant efforts to prepare 1,4-DHPs have been made in the past few years. The classical method for the preparation of these compounds is the Hantzsch reaction involving the condensation of β-ketoester, aldehyde, and ammonia [15], but some important type of derivatives, including *N*-ary-1, 4-DHPs and 5- or 6-unsubstitued 1,4-DHPs cannot be synthesized with this method. Until now, there have been few reports on the synthesis of these unsymmetrical 1, 4-DHPs [16–22]. Due to the importance of unsymmetrical 1,4-DHPs from pharmaceutical, industrial, and synthetic points of view, there still remains a high demand for the development of an efficient, low-cost, and eco-friendly protocol to assemble these compounds.

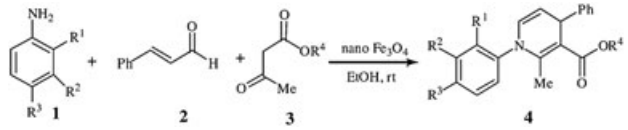
In recent years, nanocrystalline metal oxides have been increasing in importance because of their easy preparation and widespread applications as thermal insulators, humidity sensors, absorbents for gases, and destruction of hazardous chemical [23]. As their surface display both Lewis acid and Lewis base character [24], possess high surface area and more coordination sites, they are also considered as heterogenous catalysts in various organic transformations [25,26]. In particular, the magnetic nanoparticles iron oxides have attracted growing interest because of unusual properties and potential applications in diverse fields such as magnetically assisted drug delivery, magnetic resonance imaging contrast agents, hyperthermia, and magnetic separation of biomolecules [27,28]. Additionally, the magnetic property of such particles provides a convenient method for quantitative recovery of the catalyst by applying an external magnetic field [29–31].

As an extension to our previous work on the development of new synthetic methods for important heterocyclic compounds [32–38], herein, we report the use of Fe_3O_4 nanoparticles as a magnetically separable catalyst for the synthesis of 1,4-dihydropyridines by a one-pot three-component coupling of aromatic amines, α,β-unsaturated aldehydes and β-keto esters (Scheme 1).

RESULTS AND DISCUSSION

In the initial experiment, the condensation of cinnamaldehyde, aniline, and acetoacetate was chosen as the model to examine the efficiency of different catalysts, reaction

Scheme 1. Synthesis of 1,4-dihydropyridines catalyzed by magnetic nano-Fe_3O_4.



media, and the amounts of catalyst. It was showed that nearly no product could be detected, when the reaction was carried out at room temperature in ethanol for 24 h in the absence of catalysts (Table 1, entry 1), which indicated that the catalysts should be absolutely necessary for this transformation. As shown in Table 1, 11 nanocrystalline metal oxides such as MgO, CuO, In_2O_3, Al_2O_3, Y_2O_3, α-Fe_2O_3, γ-Fe_2O_3, ZnO, ZrO_2, TiO_2, and Fe_3O_4 were test for this reaction. Nano-Fe_3O_4 was found to be the most effective catalyst for this transformation, because it gave the highest yield of product (Table 1, entry 12). The effect of solvent was also investigated, and ethanol was found to be the best choice. Only trace amounts of product were observed when the reaction was run in water or in tetrahydrofuran. It was also found that the use of 10 mmol % catalyst is sufficient to promote the reaction.

Table 1

Optimization of the reaction conditions for the reaction of cinnamaldehyde, aniline, and acetoacetate.[a]

Entry	Catalyst	Catalyst amount (mol %)	Solvent	Time (h)	Yield (%)[b]
1	No		EtOH	24	0
2	CuO	10	EtOH	6	60
3	MgO	10	EtOH	6	63
4	In_2O_3	10	EtOH	6	58
5	Al_2O_3	10	EtOH	6	60
6	Y_2O_3	10	EtOH	6	59
7	α-Fe_2O_3	10	EtOH	6	65
8	γ-Fe_2O_3	10	EtOH	6	50
9	ZnO	10	EtOH	6	62
10	ZrO_2	10	EtOH	6	65
11	TiO_2	10	EtOH	6	66
12	Fe_3O_4	10	EtOH	6	70
13	Fe_3O_4	10	H_2O	10	Trace
14	Fe_3O_4	10	THF	8	Trace
15	Fe_3O_4	10	CH_3CN	8	48
16	Fe_3O_4	10	CH_2Cl_2	8	52
17	Fe_3O_4	10	AcOEt	8	55
18	Fe_3O_4	2	EtOH	6	48
19	Fe_3O_4	5	EtOH	6	51
20	Fe_3O_4	20	EtOH	6	68

[a]Conditions: cinnamaldehyde (1 mmol), aniline (1 mmol), acetoacetate (1 mmol), solvent (5 mL), and room temperature.
[b]Isolated yields.

Using these newly developed conditions, we explored the scope and limitations of this method, and the results are summarized in Table 2. Aromatic anilines with both electron-donating and electron-withdrawing groups were underwent condensation reaction with cinnamaldehyde and β-keto esters to give the corresponding 1,4-dihydropyridines in moderate to good yields. It is noteworthy to mention that the nature of the substituents on the benzene ring has shown a delicate effect on this conversion. The presence of an electron-withdrawing group on the benzene ring decreased the reactivity and gave the products in lower yields. However, aliphatic amines such as benzylamine formed the mixtures of products containing the desired compounds in low concentrations. 5,6-Unsubstituted dihydropyridines can be readily transformed into various complex heterocyclic frameworks, because the presence of C_5 C_6-unsubstituted bond enables the use of these compounds as enamine-like reagents [20]. Therefore, the present method provides a novel strategy for the preparation of a diverse array of 5,6-unsubstituted dihydropyridines.

The recyclability of the catalyst was also investigated with a model reaction of cinnamaldehyde, aniline, and acetoacetate. After each run, the catalyst was recovered from reaction mixture using an external permanent magnet, washed with ethyl acetate, dried under an infrared lamp, and then used directly in the next run without further purification. It was shown that the catalyst could be recovered and reused at least five times without significant loss of catalytic activity.

Table 2

One-pot three-component synthesis of 1,4-dihydropyridines.

Entry	R^1	R^2	R^3	R^4	Product	Time (h)	Yield (%)[a]	Ref.
1	H	H	H	Me	**4a**	6	71	[22]
2	H	OMe	H	Me	**4b**	6	72	[17]
3	H	H	Me	Me	**4c**	6	71	[17]
4	H	Me	H	Me	**4d**	6	75	[17]
5	H	H	CMe_3	Me	**4e**	6	72	
6	H	H	F	Me	**4f**	7	63	[17]
7	H	H	Br	Me	**4g**	7	65	
8	H	H	H	Et	**4h**	6	70	[20]
9	H	H	Me	Et	**4i**	6	73	[20]
10	H	OMe	H	Et	**4j**	6	75	[17]
11	H	H	OMe	Et	**4k**	6	80	[20]
12	H	Me	H	Et	**4l**	6	73	[17]
13	H	H	CMe_3	Et	**4m**	6	80	
14	Me	Me	H	Et	**4n**	6	83	[17]
15	Me	H	Me	Et	**4o**	6	65	[16]
16	H	H	F	Et	**4p**	6	66	[20]
17	H	H	Cl	Et	**4q**	7	63	[20]
18	H	Cl	H	Et	**4r**	7	62	[20]
19	H	H	Br	Et	**4s**	7	65	[20]
20	H	H	H	$CH(CH_3)_2$	**4t**	6	72	[20]
21	H	H	H	$CH_2CH{=}CH_2$	**4u**	6	73	[20]

[a]Isolated yields.

CONCLUSIONS

We have developed a simple, efficient, and general protocol for the straightforward synthesis of *N*-aryl substituted 1,4-dihydropyridines through three-component coupling reaction of aromatic amines, α,β-unsaturated aldehyde, and β-keto esters. Furthermore, the catalyst can be readily recovered with a permanent magnet and reused without significant loss of catalytic activity. We expect that this magnetic catalyst can be found application in many other industrially important catalytic processes.

EXPERIMENTAL

IR spectra were recorded with a Shimadzu FTIR-8900 spectrometer using KBr plates. ^{1}H NMR spectra were measured on a Varian 400 or a Bruker DRX-500 spectrometer using $CDCl_3$ as solvent and tetramethylsilane (TMS) as the internal standard. Elemental analyses were carried out on a Vario EL III CHNOS elemental analyzer. Commercially available reagents were used without further purification. Magnetic Fe_3O_4 nanoparticles were prepared and characterized according to the literature [39,40].

General Procedure for Synthesis of 1,4-dihydropyridines (4). A mixture of cinnamaldehyde (1 mmol), aniline (1 mmol), acetoacetate (1 mmol), and nano-Fe_3O_4 (0.023 g, 0.1 mmol) in ethanol (5 mL) was stirred at room temperature for an appropriate time (monitored by thin-layer chromatography (TLC)). After completion of the reaction, the catalyst was removed with a permanent magnet. The solvent was evaporated under reduced pressure, and the resulting residue was purified by chromatography on silica gel (hexane/ethyl acetate) to afford the corresponding pure product.

2-Methyl-1,4-diphenyl-1,4-dihydropyridine-3-carboxylic acid methyl ester (4a). This compound was obtained as brownish semisolid; IR: 2947, 1636, 1616, 1436, 1272, 1224, 1120, 1068, 1001, 952 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.15 (s, 3H), 3.57 (s, 3H), 4.68 (d, *J* = 5.6 Hz, 1H), 5.02 (dd, *J* = 7.6, 5.6 Hz, 1H), 6.13 (d, *J* = 7.6 Hz, 1H), 7.16–7.20 (m, 3H), 7.30–7.36 (m, 5H), 7.39–7.43 (m, 2H); Anal. Calcd. for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.87; H, 6.42; N, 4.43.

Methyl 1-(4-(*tert*-butyl)phenyl)-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (4e). This compound was obtained as brownish semisolid; IR: 2962, 1693, 1562, 1512, 1489, 1452, 1431, 1382, 1353, 1276, 1224, 1186, 1107, 1076, 840 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.34 (s, 9H), 2.15 (s, 3H), 3.57 (s, 3H), 4.66 (d, *J* = 5.5 Hz, 1H), 5.01 (dd, *J* = 7.5, 5.5 Hz, 1H), 6.17 (d, *J* = 7.5 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 2H), 7.18 (t, *J* = 7.0 Hz, 1H), 7.30 (t, *J* = 5.5 Hz, 2H), 7.35 (d, *J* = 7.0 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H); Anal. Calcd. for $C_{24}H_{27}NO_2$: C, 79.74; H, 7.53; N, 3.87. Found: C, 79.93; H, 7.38; N, 4.02.

1-(4-Bromophenyl)-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylic acid methyl ester (4g). This compound was obtained as brownish solid; m.p. 96–98°C; IR: 2924, 2854, 1692, 1577, 1559, 1487, 1383, 1340, 1285, 1112, 1066, 1008, 835 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.14 (s, 3H), 3.58 (s, 3H), 4.67 (d, *J* = 5.6 Hz, 1H), 5.04 (dd, *J* = 7.6, 5.6 Hz, 1H), 6.13 (d, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 2H), 7.17–7.21 (m, 1H), 7.30–7.32 (m, 4H), 7.54 (d, *J* = 8.4 Hz, 2H); Anal. Calcd. for $C_{20}H_{18}BrNO_2$: C, 62.51; H, 4.72; N, 3.65. Found: C, 62.38; H, 4.85; N, 3.46.

1-(4-*tert*-Buty-phenyl)-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylic acid ethyl ester (4m). This compound was obtained as brownish semisolid; IR: 2996, 1683, 1635, 1616, 1560, 1425, 1120, 1068, 999 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (t, *J* = 7.2 Hz, 3H), 1.34 (s, 9H), 2.16 (s, 3H), 4.02 (q, *J* = 7.2 Hz, 2H), 4.68 (d, *J* = 5.6 Hz, 1H), 5.00 (dd, *J* = 7.6, 5.6 Hz, 1H), 6.16 (d, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 2H), 7.16–7.20 (m, 1H), 7.28–7.36 (m, 4H), 7.41 (d, *J* = 8.4 Hz, 2H); Anal. Calcd. for $C_{25}H_{29}NO_2$: C, 79.96; H, 7.78; N, 3.73. Found: C, 80.08; H, 7.92; N, 3.57.

Isobutyl 2-methyl-1,4-diphenyl-1,4-dihydropyridine-3-carboxylate (4t). This compound was obtained as brownish liquid; IR: 1960, 2871, 1693, 1595, 1568, 1382, 1353, 1338, 1276, 1218, 1110, 1072, 1029, 839 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.78 (d, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 7.0 Hz, 3H), 1.77–1.85 (m,1H), 2.18 (s, 3H), 3.76 (d, *J* = 7.0 Hz, 2H), 4.69 (d, *J* = 5.5 Hz, 1H), 5.03 (dd, *J* = 7.5, 5.5 Hz, 1H), 6.13 (d, *J* = 7.5 Hz, 1H), 7.16–7.21 (m, 3H), 7.29–7.36 (m, 5H), 7.42 (t, *J* = 7.5 Hz, 2H); Anal. Calcd. for $C_{23}H_{25}NO_2$: C, 79.51; H, 7.25; N, 4.03. Found: C, 79.68; H, 7.03; N, 3.90.

Allyl 2-methyl-1,4-diphenyl-1,4-dihydropyridine-3-carboxylate (4u). This compound was obtained as yellow liquid; IR: 2931, 1693, 1595, 1566, 1452, 1382, 1355, 1315, 1276, 1218, 1110, 995, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.16 (s, 3H), 4.49–4.51 (m, 2H), 4.72 (d, *J* = 5.5 Hz, 1H), 4.50 (dd, *J* = 7.5, 5.5 Hz, 1H), 5.09–5.15 (m, 2H), 5.77–5.85 (m, 1H), 6.17 (d, *J* = 7.5 Hz, 1H), 7.17–7.21 (m, 3H), 7.29–7.32 (m, 3H), 7.34–7.37 (m, 2H), 7.40–7.44 (m, 2H); Anal. Calcd. for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.88; H, 6.55; N, 4.08.

Acknowledgments. We are grateful to the National Natural Science Foundation of China (20872025 and 21072042), Nature Science Foundation of Hebei Province (B2011205031), and the Undergraduate Scientific and Technological Innovation Project of Hebei Normal University for support of this research.

REFERENCES AND NOTES

[1] Yadav, J. S.; Antony, A.; George, J.; Reddy, B. V. S. Curr Org Chem 2010, 14, 414.

[2] Kumaravel, K.; Vasuki, G. Curr Org Chem 2009, 13, 1820.

[3] Wang, X. S.; Li, Q.; Wu, J. R.; Yao, C. S.; Tu, S. J. J Heterocycl Chem 2009, 46, 1229.

[4] Chen, J. X.; Su, W. K.; Wu, H. Y.; Liu, M. C.; Jin, C. Green Chem 2007, 9, 972.

[5] Raghuvanshi, D. S.; Singh, K. N. J Heterocycl Chem 2010, 47, 1323.

[6] Reimao, J. Q.; Scotti, M. T.; Tempone, A. G. Bioorg Med Chem 2010, 18, 8044.

[7] Sirisha, K.; Achaiah, G.; Reddy, V. M. Arch Pharm 2010, 343, 342.

[8] Cateni, F.; Zacchigna, M.; Pedemonte, N.; Galietta, L. J. V.; Mazzei, M. T.; Fossa, P.; Giampieri, M.; Mazzei, M. Bioorg Med Chem 2009, 17, 7894.

[9] Khoshneviszadeh, M.; Edraki, N.; Javidnia, K.; Alborzi, A.; Pourabbas, B.; Mardaneh, J.; Miri, R. Bioorg Med Chem 2009, 17, 1579.

[10] Kumar, A.; Sharma, S.; Tripathi, V. D.; Maurya, R. A.; Srivastava, S. P.; Bhatia, G.; Tamrakar, A. K.; Srivastava, A. K. Bioorg Med Chem 2010, 18, 4138.

[11] Edraki, N.; Mehdipour, A. R.; Khoshneviszadeh, M.; Miri, R. Drug Discov Today 2009, 14, 1058.

[12] Maiti, S.; Sridharan, V.; Menendez, J. C. J Comb Chem 2010, 12, 713.
[13] Chang, C. C.; Cao, S.; Kang, S.; Kai, L.; Tian, X. Y.; Pandey, P.; Dunne, S. F.; Luan, C. H.; Surmeier, D. J.; Silverman, R. B. Bioorg Med Chem 2010, 18, 3147.
[14] Pleiss, U. J Labelled Compd Radiopharm 2007, 50, 818.
[15] Pasunooti, K. K.; Jensen, C. N.; Chai, H.; Leow, M. L.; Zhang, D. W.; Liu, X. W. J Comb Chem 2010, 12, 577.
[16] Kantam, M. L.; Ramani, T.; Chakrapani, L.; Choudary, B. M. Catal Commun 2009, 10, 370.
[17] Das, B.; Suneel, K.; Venkateswarlu, K.; Ravikanth, B. Chem Pharm Bull 2008, 56, 366.
[18] Maiti, S.; Menendez, J. C. Synlett 2009, 2249.
[19] Moreau, J.; Duboc, A.; Hubert, C.; Hurvois, J. P.; Renaud, J. L. Tetrahedron Lett 2007, 48, 8647.
[20] Sridharan, V.; Perumal, P. T.; Avendano, C.; Menendez, J. C. Tetrahedron 2007, 63, 4407.
[21] Jiang, J.; Yu, J.; Sun, X. X.; Rao, Q. Q.; Gong, L. Z. Angew Chem Int Ed 2008, 47, 2458.
[22] Kumar, A.; Maurya, R. A.; Sharma, S.; Kumar, M.; Bhatia, G. Eur J Med Chem 2010, 45, 501.
[23] Bell, A. T. Science 2003, 299, 1688.
[24] Mirjafary, Z.; Saeidian, H.; Sadeghi, A.; Moghaddam, F. M. Catal Commun 2008, 9, 299.
[25] Hegde, M. S.; Madras, G.; Patil, K. C. Acc Chem Res 2009, 42, 704.
[26] Kahn, M. L.; Glaria, A.; Pages, C.; Monge, M.; Saint Macary, L.; Maisonnat, A.; Chaudret, B. J Mater Chem 2009, 19, 4044.
[27] Zhu, Y. H.; Stubbs, L. P.; Ho, F.; Liu, R. Z.; Ship, C. P.; Maguire, J. A.; Hosmane, N. S. Chemcatchem 2010, 2, 365.
[28] Corr, S. A.; Rakovich, Y. P.; Gun'ko, Y. K. Nanoscale Res Lett 2008, 3, 87.
[29] Shylesh, S.; Schunemann, V.; Thiel, W. R. Angew Chem Int Ed 2010, 49, 3428.
[30] Shi, F.; Tse, M. K.; Zhou, S. L.; Pohl, M. M.; Radnik, J.; Hubner, S.; Jahnisch, K.; Bruckner, A.; Beller, M. J Am Chem Soc 2009, 131, 1775.
[31] Wu, X. J.; Jiang, R.; Wu, B.; Su, X. M.; Xu, X. P.; Ji, S. J. Adv Synth Catal 2009, 351, 3150.
[32] Zhang, Z.-H.; Zhang, P.; Yang, S.-H.; Wang, H.-J.; Deng, J. J Chem Sci 2010, 122, 427.
[33] Hou, J.-T.; Liu, Y.-H.; Zhang, Z.-H. J Heterocycl Chem 2010, 47, 703.
[34] Zhang, Z.-H.; Li, J.-J.; Gao, Y.-Z.; Liu, Y.-H. J Heterocycl Chem 2007, 44, 1509.
[35] Wang, H.-J.; Ren, X.-Q.; Zhang, Y.-Y.; Zhang, Z.-H. J Braz Chem Soc 2009, 20, 1939.
[36] Wang, H.-J.; Lu, J.; Zhang, Z.-H. Monatsh Chem 2010, 141, 1107.
[37] Zhang, Z.-H.; Wang, H.-J.; Ren, X.-Q.; Zhang, Y.-Y. Monatsh Chem 2009, 140, 1481.
[38] Sun, W.-B.; Zhang, P.; Fan, J.; Chen, S.-H.; Zhang, Z.-H. Synth Commun 2010, 40, 587.
[39] Lu, H.-Y.; Yang, S.-H.; Deng, J.; Zhang, Z.-H. Aust J Chem 2010, 63, 1290.
[40] Zhang, Z.-H.; Lü, H.-Y.; Yang, S.-H.; Gao, J.-W. J Comb Chem 2010, 12, 643.