Article

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$Fe(NO_3)_3·9H_2O$ as Efficient Catalyst for One-pot Synthesis of Highly Functionalized Piperidines

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$Fe(NO_3)_3·9H_2O$ is used as an efficient and effective catalyst for the one-pot three-component synthesis of highly functionalized piperidines from aromatic aldehydes, anilines and β–ketoesters in ethanol at ambient temperature. This procedure includes some important aspects like the easy work-up, no need to column chromatography, simple and readily available precursors, and good to high yields.

Keywords: Heterocycle; Piperidine; $Fe(NO_3)_3·9H_2O$; Multi-component reaction.

INTRODUCTION

The piperidine ring system is one of the most common motifs found in numerous drugs, drug candidates and natural products such as alkaloides.[1-3] compounds with this ring exhibit anti-hypertensive,[4] antibacterial,[5] neuro-protective agents,[6,7] anticonvulsant and anti-inflammatory agents,[8,9] and also antimalarial activities.[10] Furthermore, these are intricately involved in the MAO based mechanism of Parkinson's disease[11] and as inhibitors of farnesyl transferase[12] and dihydroorate dehydrogenase[13] and also play key roles in many disease processes. Also substituted piperidines have been identified as an important class of therapeutic agents in the treatment of influenza infection,[14] cancer metastatis,[15] viral infections including AIDS,[16] and diabetes[17] (Fig. 1).

As a result, various synthetic approaches have been developed for the synthesis of these important compounds. Recently, the synthesis of highly functionalized piperidines have been reported using multi-component reactions in the presence of L-proline/TFA,[10] $InCl_3$,[18,19] bromodimethylsulfonium bromide (BDMS),[20] tetrabutylammonium tribromide (TBATB),[21] iodine,[22] cerium ammonium nitrate (CAN),[23] $ZrOCl_2·8H_2O$,[24] $BF_3·SiO_2$,[25] $Bi(NO_3)_3·5H_2O$,[26] picric acid,[27] *p*-$TsOH·H_2O$,[28] AcOH,[29] and oxalic acid dihydrate[30] as catalyst. Owing to the importance of piperidines from pharmaceutical and biological view, introduction of an efficient method for the preparation of these compounds is still in demand. As part of our continuing interest in the development of multi-component reactions,[31-34] herein we report a one-pot three (is situ five)-component synthesis of highly functionalized piperidine **4** from the reaction of aromatic aldehyde **1**, aromatic amine **2**, and β-ketoester **3** in the presence of $Fe(NO_3)_3·9H_2O$ (20 mol %) in ethanol at ambient temperature (Scheme I).

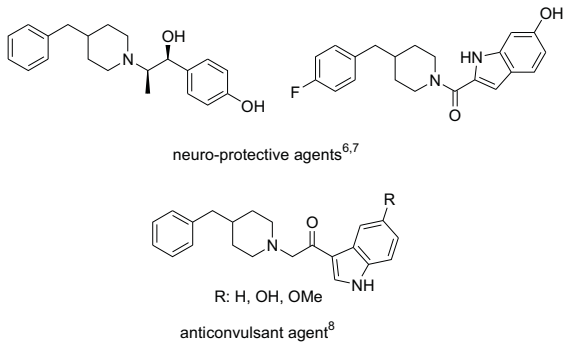
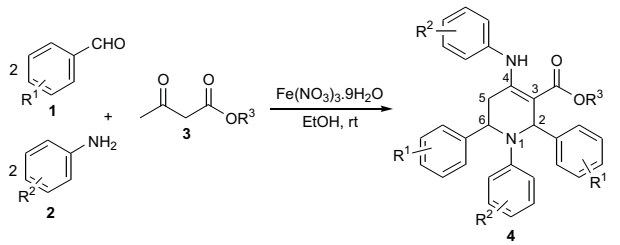


Fig. 1. Pharmaceutically active compounds containing piperidine framework.

Scheme I Synthesis of highly functionalized piperidine **4**



RESULTS AND DISCUSSION

Initially, the reaction of 4-methyl benzaldeyde, aniline and methyl acetoacetate was chosen as a model reaction for the synthesis of corresponding highly substituted piperidine **4a**. Various potential catalysts were tested in dif-

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ferent solvents at ambient temperature. As shown in Table 1, the best result was obtained in the presence of 20 mol% $Fe(NO_3)_3{\cdot}9H_2O$ in EtOH (Table 1, Entry 14). It is noteworthy that the increasing of catalyst loading to 25 mol% had no improving effect on the yield of product. When the reaction proceeded in the absence of catalyst no product was obtained, which this observation indicated that the catalyst's presence is necessary for this transformation. Low yields were obtained when water or solvent-free conditions was employed.

To investigate the generality and the scope of this one-pot three-component reaction, the optimized reaction conditions as described above was extended to various aromatic aldehyde, aromatic amine and methyl and/or ethyl acetoacetate. The results are summarized in Table 2. Various sensitive functionality groups such as Me, OMe, NO_2, F, Cl and Br were tolerated during the reaction. All reactions proceeded efficiently and cleanly and the desired products were obtained in good to excellent yields. However, no product was obtained from the reaction of *p*-dimethylamino benzaldehyde, *p*-anisidine and methyl acetoacetate (Table 2, entry 29). The structures of all compounds were characterized by comparison of IR, ^1H and ^{13}C NMR spectra with authentic samples. Also, the relative stereochemistry of these piperidines has been confirmed by single X-ray crystallography analysis in previously reported literature.[18-26,30]

In summary, an efficient and simple method has been developed for the formation of highly functionalizaed piperidines via one-pot three-component reaction catalyzed by $Fe(NO_3)_3{\cdot}9H_2O$. This methodology offered several advantages such as mild reaction conditions, simplicity in operation, good to excellent yields, simple and readily available precursors, which make it a useful and attractive process for synthesis of these important compounds.

EXPERIMENTAL

General procedure for synthesis of highly functionalized piperidine 4

First, a solution of aromatic amine (2 mmol) and β-ketoester (1 mmol) in ethanol (5 mL) was stirred for 30 min in the presence of $Fe(NO_3)_3{\cdot}9H_2O$ (20 mol%) at ambient temperature. Next, the aromatic aldehyde (2 mmol) was added and the reaction mixture was allowed to stir for appropriate time. The progress of the reaction was monitored by TLC. After completion of the reaction, the resulting precipitates were collected by filteration and washed with EtOH (3 × 2 mL) to give the pure product. Spectral data of selected products are represented below.

Table 1. The effect of different catalyst on the synthesis of piperidine **4a**[a]

Entry	Catalyst (mol%)	Solvent	Time (h)	Yield (%)[b]
1	LiCl (10)	EtOH	48	—
2	KI (10)	EtOH	48	5
3	$CuCl_2$ (10)	EtOH	48	38
4	$Al_2(SO_4)_3{\cdot}18\ H_2O$ (10)	EtOH	48	25
5	$Cu(OAc)_2{\cdot}H_2O$ (10)	EtOH	48	—
6	$AgNO_3$ (10)	EtOH	48	—
7	$Zr(NO_3)_2$ (10)	EtOH	24	35
8	$Mg(NO_3)_2{\cdot}4H_2O$ (10)	EtOH	48	10
9	$Zn(NO_3)_2{\cdot}6H_2O$ (10)	EtOH	24	30
10	$Mn(NO_3)_2{\cdot}4H_2O$ (10)	EtOH	24	50
11	$Fe(NO_3)_3{\cdot}9H_2O$ (10)	EtOH	12	72
12	$Fe(NO_3)_3{\cdot}9H_2O$ (5)	EtOH	18	55
13	$Fe(NO_3)_3{\cdot}9H_2O$ (15)	EtOH	6	84
14	$Fe(NO_3)_3{\cdot}9H_2O$ (20)	EtOH	5	91
15	$Fe(NO_3)_3{\cdot}9H_2O$ (25)	EtOH	5	90
16	$Fe(NO_3)_3{\cdot}9H_2O$ (20)	MeOH	5	87
17	$Fe(NO_3)_3{\cdot}9H_2O$ (20)	MeCN	7	70
18	$Fe(NO_3)_3{\cdot}9H_2O$ (20)	H_2O	24	30
18	$Fe(NO_3)_3{\cdot}9H_2O$ (20)	Neat	16	37
20	No Catalyst	EtOH	48	—

[a] Experimental conditions: 4-methyl benzaldehyde (2 mmol), aniline (2 mmol), and methyl acetoacetate (1 mmol), rt. [b] Isolated yield.

Methyl 1-phenyl-4-(phenylamino)-2,6-dip-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylate (4a)

White solid. ^1H NMR (400 MHz, $CDCl_3$): δ 2.25 (3H, s, CH_3), 2.32 (3H, s, CH_3), 2.75 (1H, dd, J = 15.2, 2.4 Hz, H′-5), 2.84 (1H, dd, J = 15.2, 5.6 Hz, H″-5), 3.93 (3H, s, OCH_3), 5.09 (1H, d, J = 3.1 Hz, H-6), 6.32 (2H, d, J = 8.0 Hz, ArH), 6.37 (1H, s, H-2), 6.48 (2H, d, J = 8.8 Hz, ArH), 6.60 (1H, t, J = 7.2 Hz, ArH), 7.00-7.12 (11H, m, ArH), 7.20 (2H, d, J = 8.0 Hz, ArH), 10.29 (1H, s, NH).

Ethyl 4-(3,4-dichlorophenylamino)-1-(3,4-dichlorophenyl)-2,6-dip-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylate (4i)

White solid. ^1H NMR (400 MHz, $CDCl_3$): δ 1.50 (3H, t, J = 6.4 Hz, OCH_2CH_3), 2.34 (3H, s, CH_3), 2.35 (3H, s, CH_3), 2.73 (1H, d, J = 15.2 Hz, H′-5), 2.90 (1H, dd, J = 15.2, 5.6 Hz, H″-5), 4.31-4.40 (1H, m, OCH_aH_b), 4.46-4.54 (1H, m, OCH_aH_b), 5.08 (1H, br s, H-6), 6.16 (2H, d, J = 7.2 Hz, ArH), 6.36 (1H, s, H-2), 6.43 (2H, d, J = 7.8 Hz, ArH), 6.96-7.23 (10H, m, ArH), 10.24 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.8 (OCH_2CH_3), 21.6 (CH_3), 21.8 (CH_3), 33.4 (C-5), 55.3 (C-2), 58.2 (C-6), 59.8 (OCH_2CH_3), 98.9 (C-3), 108.3, 114.6, 119.2, 123.5, 123.5, 126.9,

Table 2. The synthesis of highly substituted piperidine **4a-4ab**

Entry	R^1	R^2	R^3	Product	Time (h)	Yield (%)[a]	m.p. (lit. reported)Ref.,[b]
1	4-Me	H	Me	**4a**	5	91	213-216 (215-217)[22]
2	4-Me	H	Et	**4b**	5	89	226-228 (228-231)[22]
3	4-Me	4-Br	Me	**4c**	7	92	227-230 (230-232)[22]
4	4-Me	4-OMe	Me	**4d**	6	87	221-224 (225-226)[20]
5	4-Me	4-OMe	Et	**4e**	6	89	219-222 (221-224)[23]
6	4-Me	4-Me	Me	**4f**	5	93	203-205 (206-208)[22]
7	4-Me	4-Me	Et	**4g**	6	90	169-171 (169-171)[30]
8	4-Me	4-F	Et	**4h**	7	91	183-185 (183-185)[28]
9	4-Me	3,4-di-Cl	Et	**4i**	7	84	173-175 (173-175)[28]
10	4-OMe	H	Et	**4j**	8	77	165-168 (166-168)[28]
11	4-OMe	H	Me	**4k**	7	85	182-184 (187-188)[20]
12	4-OMe	4-Cl	Me	**4l**	12	76	194-196 (194-195)[23]
13	4-OMe	4-Br	Me	**4m**	8	89	175-177 (178)[10]
14	4-F	H	Me	**4n**	6	93	180-182 (180)[10]
15	4-F	4-OMe	Me	**4o**	8	84	200-202 (204-205)[23]
16	4-F	4-Me	Me	**4p**	5	88	200-202 (200-202)[33]
17	H	H	Me	**4q**	6	92	168-170 (169-171)[20]
18	H	H	Et	**4r**	6	90	170-173 (174-175)[20]
19	H	4-Br	Et	**4s**	8	91	197-199 (196-198)[30]
20	H	4-OMe	Et	**4t**	6	88	178-181 (179-181)[28]
21	3-Cl	H	Me	**4u**	6	89	216-218 (220-221)[23]
22	3-Cl	4-Cl	Et	**4v**	7	84	185-188 (190)[10]
23	4-Cl	H	Me	**4w**	7	91	190-191 (189-191)[20]
24	4-Br	4-Cl	Me	**4x**	9	78	158-161 (160-163)[10]
25	3-Br	H	Et	**4y**	6	86	166-168 (164-167)[29]
26	4-NO_2	H	Me	**4z**	9	45	235-237 (239-241)[22]
27	H	4-Me	Et	**4aa**	7	88	194-196 (194-196)[29]
28	4-Cl	4-F	Et	**4ab**	8	83	218-220 (219-222)[27]
29	4-NMe_2	4-OMe	Me	No reaction	24	—	—

[a] Isolated yield. [b] The references of known products in the literature.

127.2, 127.5, 127.4, 128.2, 128.3, 128.7, 131.5, 131.9, 137.1, 138.0, 138.4, 142.2, 143.3, 146.0, 155.4 (C-4), 168.1 (C=O).

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