Res Chem Intermed (2015) 41:9863–9869
DOI 10.1007/s11164-015-1993-6

Citric acid, a green catalyst for the one-pot, multi-component synthesis of highly substituted piperidines

Zahra Madanifar[1] · Malek-Taher Maghsoodlou[1] · Mehrnoosh Kangani[1] · Nourallah Hazeri[1]

Received: 16 September 2014 / Accepted: 2 March 2015 / Published online: 2 April 2015

Abstract Citric acid has been used as a green and efficient catalyst for one-pot, multi-component synthesis of highly substituted piperidines by condensation of aromatic aldehydes, aromatic amines, and β-ketoesters in MeOH at ambient temperature. This method has several advantages including use of a nonhazardous and inexpensive catalyst, easy work-up, clean reaction conditions, and high yields.

Keywords Citric acid · Green catalyst · Highly substituted piperidines · β-Ketoesters

Introduction

Functionalized piperidine rings are found in naturally occurring alkaloids and in anti-tumor and antibiotic drugs [1–6]. Simple derivatives of the substituted piperidine molecule L-pipecolic acid are constituents of plants, fungi, and human physiological fluids [7–9]. In particular, C-2 and C-6-substituted piperidine molecules isolated from extracts of *Dendrobates speciosus* (a Panamanian poison frog) have a range of activity, for example cytotoxic, antifungal, hemolytic, and anti-HIV [10–12] (Fig. 1). Numerous methods have recently been reported for synthesis of highly substituted piperidines by reaction of aromatic aldehydes, amines, and acetoacetic ester with a variety of catalysts, for example bismuth nitrate [13], molecular iodine [14], bromodimethylsulfonium bromide (BDMS) [15], tetrabutylammonium tribromide (TBATB) [16], $InCl_3$ [17], CAN [18], $ZrOCl_2.8H_2O$ [19], and picric acid [20]. Although different approaches have been reported, these methods have many limitations, for example use of expensive catalysts, in excessive amounts, at elevated

✉ Malek-Taher Maghsoodlou
mt_maghsoodlou@chem.usb.ac.ir

[1] Department of Chemistry, University of Sistan and Baluchestan, P.O. Box 98135-674, Zahedan, Iran

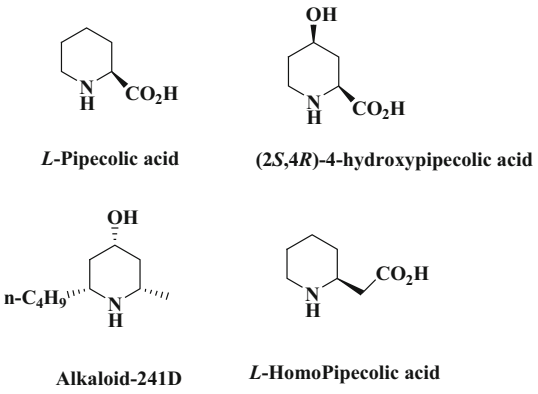


Fig. 1 Substituted piperidine molecules

temperatures, long reaction times, hazardous organic solvents and other reagents, and low yields. Hence, the development of novel methods for synthesis of functionalized piperidines is very important, because of their potential biological and pharmaceutical activity.

Citric acid is a weak organic acid with the formula $C_6H_8O_7$ (Fig. 2). It is a natural preservative which occurs naturally in citrus fruits and is also used to add an acidic or sour taste to food and drinks. In continuation of our research on green catalysts [21–24], we report herein a green synthesis of highly substituted piperidines in the presence of citric acid as catalyst in MeOH at ambient temperature (Scheme 1).

Experimental

Melting points and IR spectra were measured on an Electrothermal 9100 apparatus and a Jasco FT-IR-460 plus spectrometer, respectively. ^{1}H NMR spectra were acquired with a Bruker DRX-400 Advance instrument with $CDCl_3$ as solvent. All reagents and solvents were obtained from Merck and Aldrich and used without further purification. TLC was performed on Polygram SILG/UV 254 silica gel plates.

General procedure for synthesis of highly functionalized piperidines

First, a solution of aromatic amine **2** (2 mmol) and β-ketoester **3** (1 mmol) in MeOH (5 mL) was stirred for 20 min in the presence of citric acid (20 mol%) at ambient

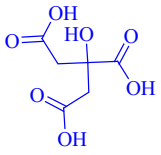
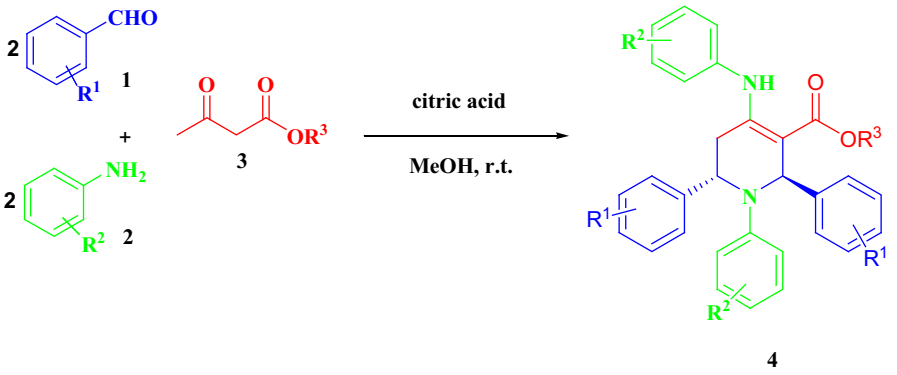


Fig. 2 Structure of citric acid



Scheme 1 Synthesis of piperidines in the presence of citric acid as green catalyst in MeOH at ambient temperature

temperature. Next, the aromatic aldehyde **1** (2 mmol) was added and the reaction mixture was stirred for the appropriate time. After completion of the reaction, as monitored by TLC, the solid obtained was isolated by filtration and washed with MeOH (3 × 2 mL) to give the pure product **4**. Physical and spectral data for selected products are reported below.

All of the products are known. Selected spectroscopic data of one known product is given below:

Ethyl 1,2,5,6-tetrahydro-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-2,6-diphenylpyridine-3-carboxylate (4e) White solid; m.p = 179–181 °C; IR (KBr, cm^{-1}) ν = 3295 (NH), 1648 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48(t, *J* = 7.0 Hz, 3H), 2.68 (dd, *J* = 15.1, 2.4 Hz,1H), 2.83 (dd, *J* = 15.1, 5.6 Hz, 1H), 3.69 (s,3H), 3.78 (s, 3H), 4.32–4.38 (m, 1H), 4.43–4.49 (m, 1H), 5.09 (d, *J* = 3.2 Hz, 1H), 6.24 (d, *J* = 8.8 Hz, 2H), 6.38 (s,1H), 6.48 (d, *J* = 9.2 Hz, 2H), 6.64 (d, *J* = 8.4 Hz, 2H), 6.70 (d, *J* = 9.2 Hz, 2H), 7.20–7.37(m, 10H), 10.18 (s, 1H) ppm.

Ethyl 4-(4-bromophenylamino)-1-(4-bromophenyl)-1,2,5,6-tetrahydro-2,6-diphenylpyridine-3-carboxylate (4h) White solid; m.p. 245–246 °C; IR (KBr, cm^{-1}) ν = 3248 (NH), 1648 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) : δ = 1.50(t, *J* = 6.8 Hz, 3H), 2.74 (d, *J* = 15.2 Hz,1H), 2. 89 (dd, *J* = 15.2, 5.6 Hz,1H), 4.35–4.40 (m,1H), 4.46–4.52 (m, 1H), 5.13 (d, *J* = 4.0 Hz, 1H), 6.14 (d, *J* = 8.0 Hz, 2H), 6.41 (s, 1H), 6.42 (d, *J* = 8.0 Hz, 2H), 7.14–7.34 (m, 14H), 10.26 (s, 1H) ppm.

Ethyl 4-(*p*-tolylamino)-1,2,5,6-tetrahydro-1,2,6-tri-*p*-tolylpyridine-3-carboxylate (4m) White solid; m.p. 169–171 8 °C; IR (KBr, cm^{-1}) ν = 3256 (NH), 1656 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.49 (t, *J* = 7.0 Hz, 3H), 2.20 (s, 3H), 2.31 (s, 3H), 2.36 (s, 3H), 2.38 (s, 3H), 2.78 (dd, *J* = 15.1, 2.4 Hz,1H), 2.87 (dd, *J* = 15.1, 5.6 Hz, 1H,), 4.37 (dq, *J* = 10.4, 7.2 Hz, 1H), 4.48 (dq, *J* = 10.4, 6.8 Hz, 1H), 5.13 (d, *J* = 3.6 Hz,1H), 6.23 (d, *J* = 8.4 Hz, 2H), 6.42 (s, 1H), 6.49 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 10.8 Hz, 2H), 6.93 (d, 2H, *J* = 7.6 Hz), 7.08–7.29 (m, 8H), 10.26 (s, 1H) ppm.

Ethyl 2,6-bis(4-methoxyphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4n) White solid; m.p. 165–168 °C; IR (KBr, cm^{-1}) $\nu = 3270$ (NH), 1656 (C=O);^{1}H NMR (400 MHz, $CDCl_3$) : $\delta = 1.50$ (t, $J = 7.2$ Hz, 3H), 2.82 (dd, $J = 15.2$, 2.4 Hz, 1H), 2.91 (dd,$J = 15.2$, 5.6 Hz, 1H), 3.82 (s, 3H), 3.83 (s,3H), 4.39 (dq, $J = 10.8$, 7.2 Hz, 1H), 4.52(dq, $J = 10.8$, 7.0 Hz, 1H), 5.13 (d, $J = 2.8$ Hz,1H), 6.40 (d, $J = 6.8$ Hz, 2H), 6.42 (s, 1H),6.57 (d, $J = 8.4$ Hz, 2H), 6.65 (t, $J = 7.2$ Hz, 1H), 6.84–6.88 (m, 4H), 7.09–7.29 (m, 9H),10.35 (s, 1H) ppm.

Results and discussion

In continuation of our work on the synthesis of heterocycles, especially piperidines [25–27], we have used citric acid as an efficient and green catalyst for one-pot, three-component (in situ five-component) synthesis of highly functionalized piperidines in MeOH at ambient temperature (Scheme 1). First, the reaction between benzaldehyde (2 mmol), aniline (2 mmol), and methyl acetoacetate (1 mmol) was chosen as model system. Initially, a control experiment confirmed that the reaction did not proceed in the absence of a catalyst (Entry 1, Table 1). The model reaction was then performed in the presence of different catalysts, $PrCl_3{\cdot}6H_2O$, fumaric acid, salicylic acid, and citric acid, in MeOH (Table 1). Catalyst reactivity in different solvents and amount of catalyst were also investigated (Tables 2, 3).

Several reactions between substituted benzaldehydes, anilines, and methyl or ethyl acetoacetate were examined under the optimized conditions; the results are summarized in Table 4. Benzaldehydes with electron-withdrawing and electron-releasing groups reacted efficiently with anilines to give the corresponding piperidines in good to high yields.

On the basis of the literature [13–18], the mechanism proposed for formation of piperidine **4** is illustrated in Scheme 2. First, the β-ketoester **2** and aldehyde **1** react with aniline **3** in the presence of citric acid to give the enamine **5** and imine **6**, respectively. Next, reaction between the enamine **5** and imine **6** leads to the intermediate **7** via an intermolecular Mannich-type reaction. The intermediate **7** reacts with aldehyde **1** to generate intermediate **8**. Tautomerization of **8** then

Table 1 Synthesis of piperidine in the presence of different catalysts

Entry	Catalyst (mol%)	Solvent	Time (h)	Isolated yield (%)
1	No catalyst	MeOH, r.t.	48	–
2	$PrCl_3{\cdot}6H_2O$ (20)	MeOH, r.t.	24	45
3	Fumaric acid (20)	MeOH, r.t.	24	38
4	Salicylic acid (20)	MeOH, r.t.	48	–
5	Citric acid (20)	MeOH, r.t.	24	80

Table 2 Optimization of the amount of catalyst for synthesis of piperidine

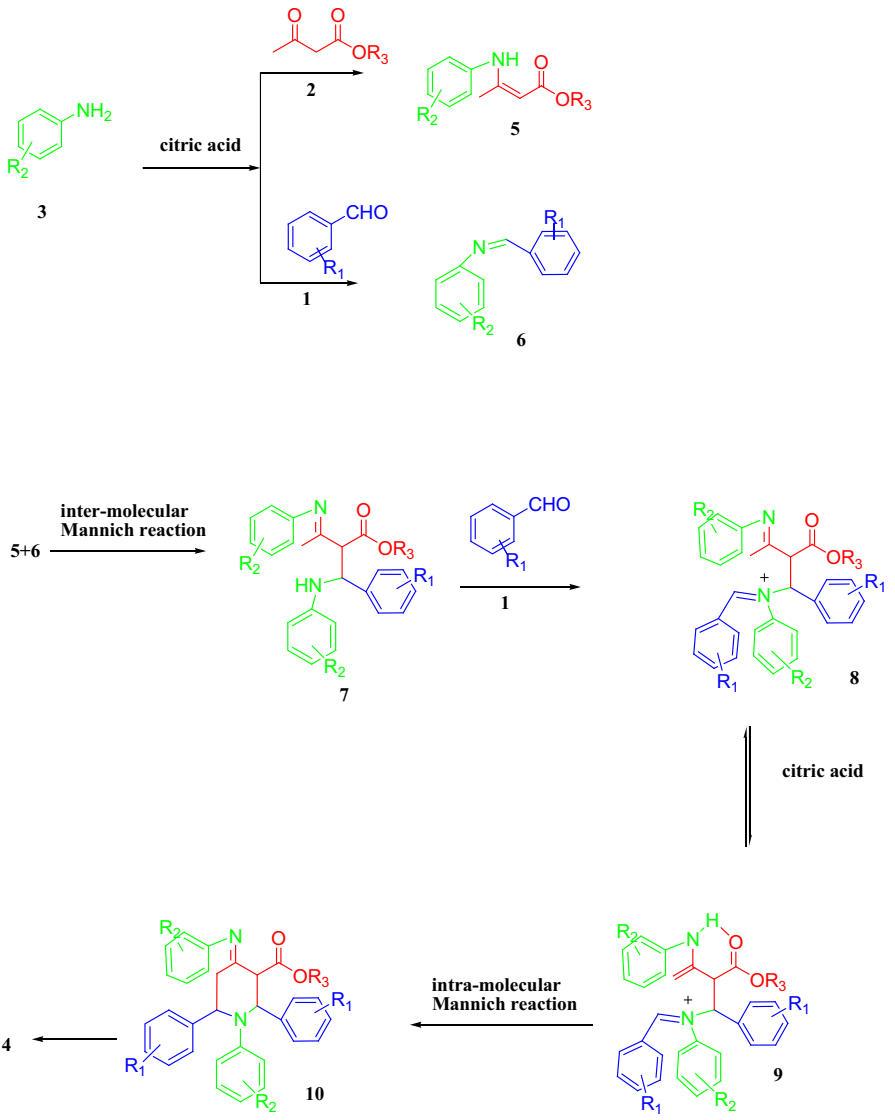
Entry	Catalyst (mol%)	Solvent	Time (h)	Isolated yield (%)
1	5	MeOH, r.t.	24	32
2	10	MeOH, r.t.	24	47
3	15	MeOH, r.t.	24	50
4	17	MeOH, r.t.	24	65
5	20	MeOH, r.t.	24	80
6	25	MeOH, r.t.	24	60
7	30	MeOH, r.t.	24	57
8	No catalyst	MeOH, r.t.	24	–

Table 3 Synthesis of piperidine in the presence of different solvents

Entry	Catalyst (mol%)	Solvent	Time (h)	Isolated yield (%)
1	20	EtOH, r.t.	24	60
2	20	MeOH, r.t.	24	80
3	20	CH_3CN, r.t.	24	–
4	20	$CHCl_3$, r.t.	24	50
5	20	H_2O, r.t.	24	–
6	20	Solvent-free	48	45

Table 4 Synthesis of highly functionalized piperidines in the presence of citric acid as catalyst in MeOH

Entry	R^1	R^2	R^3	Product	Time (h)	Isolated yield (%)	m.p. (lit. reported) [25–27]
1	H	H	Me	**4a**	8	82	171–173 (169–171)
2	4-Me	H	Me	**4b**	7	75	211–213 (212–214)
3	4-Cl	H	Me	**4c**	7	93	190–191 (189–191)
4	3-NO_2	H	Me	**4d**	6	70	182–184 (182–183)
5	H	4-OMe	Et	**4e**	6	92	179–181 (179–181)
6	H	4-Cl	Et	**4f**	6	70	202–204 (202)
7	H	H	Et	**4g**	8	80	173–176 (174–175)
8	H	4-Br	Et	**4h**	6	72	245–246 (247)
9	3-Br	4-F	Et	**4i**	8	75	187–188 (189)
10	3-Br	4-OMe	Et	**4j**	10	95	198–200 (198–199)
12	H	4-F	Me	**4k**	17	69	173–175 (172–175)
13	4-Cl	4-Cl	Me	**4l**	6	83	188–190 (189–191)
14	4-Me	4-Me	Et	**4m**	10	85	169–171 (169–171)
15	4-OMe	H	Et	**4n**	12	85	165–168 (166–168)



Scheme 2 Proposed mechanism for synthesis of highly function piperidines in the presence of citric acid as catalyst in MeOH at ambient temperature

generates intermediate **9**, which immediately undergoes intramolecular Mannich-type reaction to produce intermediate **10**. In the final step, tautomerization of the intermediate **10** generates the desired piperidine **4**, because of conjugation with the ester group.

Conclusion

A highly efficient method has been developed for synthesis of highly function piperidines by use of citric acid as catalyst at ambient temperature in MeOH. This procedure has the advantages of high yield, operational simplicity, nonhazardous catalyst, short reaction time, and minimum pollution of the environment.

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