Iranian Journal of Organic Chemistry Vol. 13, No. 1(2021) 3043-3048

A Simple and one-pot synthesis of highly functionalized piperidines in the presence of an organoacid catalyst under mild conditions

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Received: November 2020; Revised: November 2020; Accepted: January 2021

Abstract: Synthesis of piperidine derivatives by multicomponent reaction between aromatic aldehydes, aromatic amines, and β-ketoesters in the presence of lactic acid (2-hydroxy propanoic acid), as an efficient catalyst in MeOH at 45°C temperature is described. This one-pot methodology offers several advantages such as the use of an inexpensive catalyst, easy access, nonhazardous catalyst, clean work-up, excellent yields, short reaction time, and environmentally mild conditions. In this work was reported the multicomponent (MCRs) synthesis of functionalized tetrahydropyridines with potential biological activity using inexpensive and commercially available material in a one-pot reaction.

Keywords: Lactic acid, β-Ketoesters, Piperidine derivatives, Multicomponent reactions, Catalyst.

Introduction

The synthesis of highly functionalized piperidines is an important synthetic transformation as these scaffolds are found to form a very important core in numerous natural products [1], synthetic pharmaceuticals [2], and a wide variety of biologically active compounds [3]. A large number of compounds bearing piperidine scaffold have entered preclinical and clinical trials over the last few years [4]. In particular, 1,4-disubstituted piperidine scaffolds find useful applications as established drugs [5] and exhibit anti-hypertensive [6], antibacterial [7], antimalarial [8], anticonvulsant, and antiinflammatory activities [9].

Multicomponent reactions (MCRs) have emerged as efficient and powerful tools in modern synthetic organic chemistry because the synthesis of complex organic molecules from simple and readily available substrates can be achieved in a very fast and efficient manner without the isolation of any intermediate [10-12].

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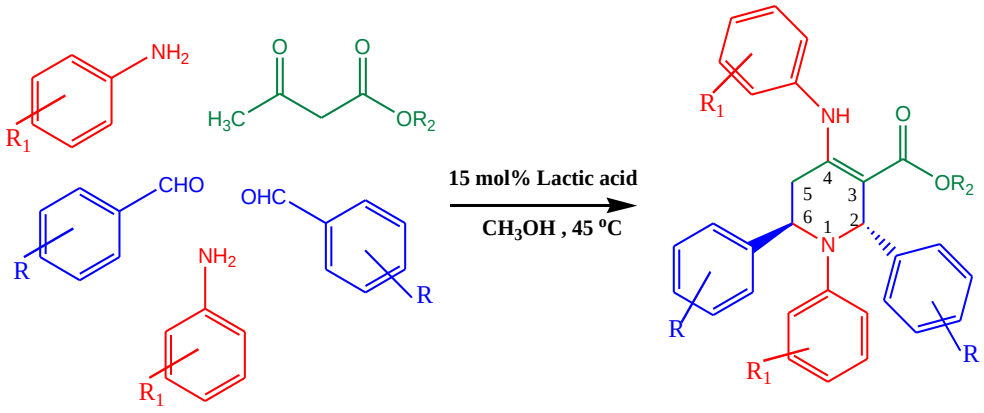
Therefore, developing new MCRs and improving known MCRs are popular areas of research in organic synthesis. In this work multicomponent reaction was reported between aromatic aldehydes, aromatic amines, and β-ketoesters in the presence of lactic acid, as a green and natural catalyst in MeOH at 45°C temperature (Scheme 1). Lactic acid as a Bronsted acid catalyst is safe, easy to handle, environmentally benign and presents fewer disposal problems. In recent years, the highly functionalized tetrahydropyridines were reported using plethora of reagents, such as a combination of L-proline/TFA,[13] bromodimethyl sulfonium bromide (BDMS),[14] tetrabutyl ammonium tribromide (TBATB),[15] molecular iodine,[16] indium chloride ($InCl_3$),[17] zirconium oxy chloride ($ZrOCl_2$),[18] and ceric ammonium nitrate (CAN).[19] Although these methods have their own merits, but suffer from the drawbacks with respect to reaction time, cost of reagents, and reaction work-ups. Consequently, this one-pot reaction still requires an efficient protocol for the synthesis of tetrahydropyridine derivatives. This catalyst does not

need any special precautions for preparation, handling or storage, and it can be stored at ambient temperature for months without losing its catalytic activity. This spurred us to investigate the synthesis of highly functionalized tetrahydropyridines via one-pot multicomponent reaction using lactic acid as a catalyst (Scheme **1**).



Scheme 1: Synthesis of piperidine derivatives in the presence of lactic acid.

Result and Discussion

In this study, the one-pot reaction of benzaldehyde and aniline with ethyl acetoacetate (2:2:1 ratio) was examined using lactic acid as catalyst under the mild conditions as a model reaction. The reaction proceeded to afford the desired functionalized tetrahydropyridines in good yield (Table **1**). In order to enhance the yield, the reaction condition is optimized using under different temperature and amount of catalyst. The observed results are summarized in Table **1**. As shown in Table **1**, the shortest time and best yield were achieved at 45°C. In this reaction was examined the amount of catalyst required for this reaction under the above condition. The reaction did not proceed without catalyst even at prolonged reaction time (48 h). It was found that when increasing the amount of the lactic acid from 5 to 10, 15, and 20 mol %, the yields also increased (Table **1**). A further increasing of the catalyst loading (above 15 mol %) does not affect the yield. Therefore, 15 mol% of lactic acid in polar solvent is sufficient to push this reaction forward.

Choices of solvents also play an important role in the multicomponent reaction. We also investigated the effect of solvent in this reaction. Various solvents, such as ethanol, methanol, ethyl acetate, dichloromethane, and water were used for this reaction at their respective reflux condition. However, solvents like ethyl acetate, and dichloromethane afforded the product in trace yield. But, no reaction was found when water used as solvent. Therefore, solvents like methanol or ethanol are the suitable solvents for the present investigation.

After that, the study was extended to the application of lactic acid in synthesis of substituted tetrahydropyridines using various aromatic aldehydes and amine with ethyl/methyl acetoacetate. The results are listed in Table **2**.

A probable mechanistic pathway for this five-component reaction is outlined in Scheme 2, which is in analogy to the established mechanism as reported in the literature [18, 19]. Lactic acid can serve as a Bronsted acid catalyst for the reaction of aniline and β-ketoester or aromatic aldehyde to give the corresponding enamine (I) or imine (II), respectively. The subsequent attack of enamine on the activated imine, followed by inter- and intra-molecular Mannich-type reactions under the reaction conditions, would eventually afford the final functionalized piperidine scaffold.

Table 1: Optimizing of the amount of catalyst and temperature in one-pot synthesis of Piperidine derivatives.

Entry	Catalyst (mol%)	Temprature (°C)	Time (h)	Isolated Yield(%)
1	5	45	8	58
2	10	45	5	70
3	**15**	**45**	**5**	**85**
4	20	45	5	85
5	15	25	12	30
6	15	35	5	75
7	15	60	5	64
8	-	45	48	0

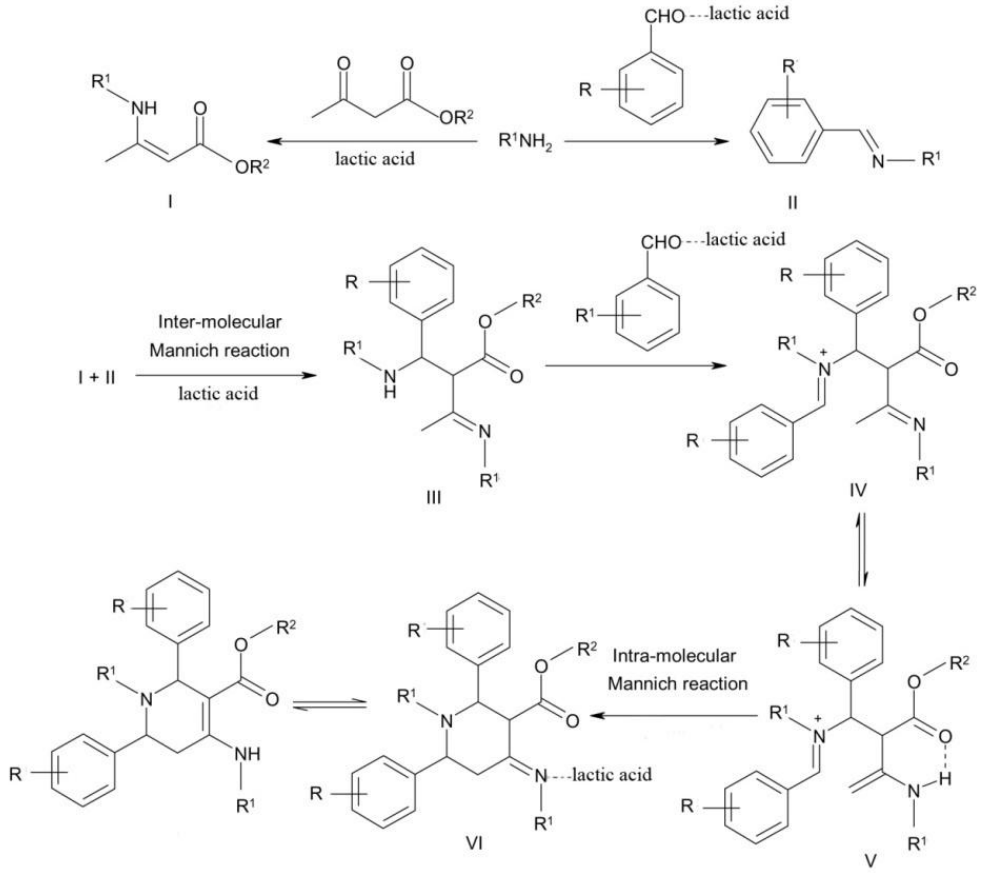
Table 2: Synthesis of Piperidine derivatives in the presence of lactic acid.

Entry	R	R_1	R_2	Time (h)	Yield (%)	Obs.m.p (lit.reported) [Ref]
1	H	H	Ethyl	5	85	173-175 (174-175) [14]
2	4-Nitro	H	Ethyl	5	90	245-247 (247-250) [19]
3	H	4-Methoxy	Ethyl	5	87	181-183 (179-181) [20]
4	H	4-Chloro	Ethyl	8	65	200-202 (202) [20]
5	H	4-Bromo	Ethyl	8	70	245-247 (247) [21]
6	4-Methoxy	H	Ethyl	7	76	167-170 (166-168) [21]
7	4-Bromo	4-Bromo	Methyl	7	78	148-150 (149) [22]
8	4-Chloro	4-Chloro	Methyl	6	85	188-190 (189-191) [20]
9	4-Nitro	H	Methyl	6	87	236-238 (239-241) [16]
10	4-Nitro	4-Methoxy	Methyl	5	90	198-200 (198-199) [18]
11	H	4-Bromo	Methyl	7	76	181-183 (179-181) [23]
12	H	4-Methoxy	Methyl	6	80	178-180 (179-181) [16]
13	4-Chloro	4-Methoxy	Methyl	5	92	161-163 (162-163) [13]
14	4-Chloro	H	Methyl	6	85	190-192 (189-191) [22]

Table 3: Comparison result of lactic acid with the reported catalysts in literature for the synthesis of highly functionalized piperidines.

Entry	Catalyst	Solvent	Yield(%)	Reference
1	TBATB	EtOH	78	[15]
2	$InCl_3$	EtOAc	50	[3]
3	CAN	EtOAc	85	[19]

4	I_2	MeOH	84	[16]
5	Oxalic acid dihydrate	EtOH	81	[21]
6	Lactic acid	MeOH	92	This work



Scheme 2: A plausible mechanism for the one-pot synthesis of functionalized piperidines.

Conclusion

In continuation of our research on heterocyclic synthesis[24-27], an efficient protocol for one-pot synthesis of functionalized tetrahydropyridines was developed by reaction between various aromatic aldehydes, aromatic amines and β-ketoesters in the presence of lactic acid (2-hydroxy propanoic acid), as a catalyst under mild thermally conditions. In this study, a straightforward and simple method for the synthesis of highly functionalized piperidines by one-pot multicomponent reaction was introduced using readily available starting materials under catalysis of lactic acid.

Experimental

General

Melting points and infrared (IR) spectra of all compounds were measured on an Electrothermal 9100 apparatus and a JASCO FT/IR 460 Plus spectrometer, respectively. The ^{1}HNMR spectra were recorded on a BRUKER DRX–400 AVANCE instrument with $CDCl_3$ as solvent at 400.1 MHz. All reagents and

solvents obtained from Aldrich and Merck were used without further purification.

Typical procedure for synthesis of Piperidine derivatives

A mixture of ethyl acetoacetate (1.0 mmol), aniline (2 mmol), and lactic acid (15 mol %) in 20 mL of methanol was stirred at 45°C for 20 minute, then benzaldehyde (2.0 mmol), was added and stirring was continued up to completion of the reaction as monitored by TLC.

After completion of the reaction, the reaction mixture was washed with H_2O (3× 10 mL). The catalyst is solvable in water and was removed from the reaction mixture. Then, the residue was recrystallized from EtOH. The structures of the synthesized compounds were characterized by their IR, melting points and ^{1}H NMR spectra and were found to be identical with data described in the literature.

Ethyl 1,2,5,6-tetrahydro-1,2,6-triphenyl-4-(phenylamino)pyridine-3-carboxylate (Table 2, entry 1):

Yellow solid, IR (KBr): ν 3260 (NH), 1652 (C=O) cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.31 (1H, s, NH), 7.06 – 7.37 (9H, m, Ar-H), 6.62 (1H, t, *J* = 7.2 Hz, Ar-H), 6.54 (2H, d, *J* = 8.4 Hz, Ar-H), 6.48 (1H, s, CH), 6.28-6.30 (4H, m, Ar-H), 5.17 (1H, d, *J* = 4.0 Hz, CH), 4.44-4.51 (1H, m, OCH_2), 4.31-4.39 (1H, m, OCH_2), 2.89 (1H, dd, *J* = 15.2, 5.6 Hz, CH_2), 2.78 (1H, dd, *J* = 15.2, 2.4 Hz, CH_2), 1.49 (3H, t, *J* = 7.1Hz, OCH_2CH_3).

Ethyl 4-(4-bromophenylamino)-1-(4-bromophenyl)-1,2,5,6-tetrahydro-2,6-diphenylpyridine-3-carboxylate (Table 2, entry 5):

White solid, IR (KBr): ν 3240 (NH), 1652 (C=O) cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.25 (1H, s, NH), 7.16 – 7.31 (14H, m, Ar-H), 6.60 (2H, d, J = 8.1 Hz, Ar-H), 6.39 (1H, s, CH), 6.15 (2H, d, *J* = 8.1 Hz, Ar-H), 5.13 (1H, d, J = 4.0 Hz, CH), 4.42-4.50 (1H, m, OCH_2), 4.33-4.41 (1H, m, OCH_2), 2.84 (1H, dd, *J* = 15.2, 5.6 Hz, CH_2), 2.73 (1H, d, *J* = 15.2 Hz, CH_2), 1.51 (3H, t, *J* = 7.1 Hz, OCH_2CH_3).

Ethyl 1,2,5,6-tetrahydro-2,6-bis(4-methoxyphenyl)-1-phenyl-4-(phenylamino)pyridine-3-carboxylate (Table 2, entry 6):

Yellow solid, IR (KBr): ν 3335 (NH), 1658 (C=O) cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.45 (1H, s, NH), 7.07 – 7.26 (9H, m, Ar-H), 6.80-6.85 (4H, m, Ar-H), 6.61 (1H, t, *J* = 7.0, Ar-H), 6.52 (2H, d, *J* = 8.4, Ar-H), 6.40 (1H, s, CH), 6.37 (2H, d, *J* = 6.8, Ar-H), 5.11 (1H, d, J = 2.8Hz, CH), 4.50 (1H, dq, *J* = 10.8, 7.0Hz, OCH_2), 4.37 (1H, dq, *J* = 10.8, 7.1Hz, OCH_2), 3.81 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 2.91(1H, dd, J = 15.3, 5.8Hz, CH_2), 2.82 (1H, d, J = 15.3, 2.3 Hz, CH_2), 1.50 (3H, t, *J* = 7.2Hz, OCH_2CH_3).

Methyl 2,6-bis(4-chlorophenyl)-1,2,5,6-tetrahydro-1-phenyl-4-(phenylamino)pyridine-3-carboxylate (Table 2, entry 14):

White solid, IR (KBr): ν 3235 (NH), 1680 (C=O) cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.27 (1H, s, NH), 7.03 – 7.27 (13H, m, Ar-H), 6.66 (1H, t, *J* = 7.0, Ar-H), 6.59 (2H, d, *J* = 8.0, Ar-H), 6.43 (1H, s, CH), 6.39 (2H, d, *J* = 7.8, Ar-H), 5.16 (1H, d, *J* = 3.6Hz, CH), 3.93 (3H, s, OCH_3), 2.86 (1H, dd, *J* = 15.2, 5.6 Hz, CH_2), 2.82 (1H, dd, J = 15.2, 2.4 Hz, CH_2).

References

[1] Viegas, C.; Bolzani, J. V. S.; Furlan, M.; Barreiro, E. J.; Young, M. C. M.; Tomazela, D.; Eberlin, M. N. *J. Nat. Prod*. **2004**, 67, 908.

[2] Breman, J.; Egan, A.; Keusch, G. *Am. J. Trop. Med. Hyg*. **2001**, 64, iv.

[3] Clarke, P. A.; Zaytzev, A. V.; Whitwood, A. C. *Tetrahedron Lett*. **2007**, 48, 5209.

[4] Kamei, K.; Maeda, N.; Katswagi-Ogino, R.; Koyamaa, M.; Nakajima, M.; Tatsuoka, T.; Ohno, T.; Inone, T. *Bioorg. Med. Chem. Lett*. **2005**, 15, 2990.

[5] Yevich, J. P.; Yocca, F. D. *Curr. Med. Chem*. **1997**, 4, 295–312.

[6] Petit, S.; Nallet, J. P.; Guillard, M.; Dreux, J.; Chermat, R.; Poncelet, M.; Bulach, C.; Simon, P.; Fontaine, C.; Barthelmebs, M.; Imbs, J. L. *Eur. J. Med. Chem*. **1991**, 26, 19.

[7] Zhou, Y.; Gregor, V. E.; Ayida, B. K.; Winters, G. C.; Sun, Z.; Murphy, D.; Haley, G.; Bailey, D.; Froelich, J. M.; Fish, S.; Webber, S. E.; Hermann, T.; Wall, D. *Bioorg. Med. Chem. Lett*. **2007**, 17, 1206.

[8] Misra, M.; Pandey, S. K.; Pandey, V. P.; Pandey, J.; Tripathi, R.; Tripathi, R. P. *Bioorg. Med. Chem*. **2009**, 17, 625.

[9] Bin, H.; Crider, A. M.; Stables, J. P. *Eur. J. Med. Chem*. **2001**, 36, 265.

[10] Huma, H. Z. S.; Halder, R.; Kalra, S. S.; Das, J.; Iqbal, J. *Tetrahedron Lett*. **2002**, 43, 6485.
[11] Bora, U.; Saikia, A.; Boruah, R. C. *Org. Lett*. **2003**, 5, 435.
[12] Dallinger, D.; Gorobets, N. Y.; Kappe, C. O. *Org. Lett*. **2003**, 5, 1205.
[13] Misra, M.; Pandey, S. K.; Pandey, V. P.; Pandey, J.; Tripathi, R.; Tripathi, R. P. *Bioorg. Med. Chem*. **2009**, 17, 625.
[14] Khan, A. T.; Parvin, T.; Choudhary, L. H. *J. Org. Chem*. **2008**, 73, 8398.
[15] Khan, A. T.; Lal, M.; Khan, M. M. *Tetrahedron Lett*. **2010**, 51, 4419.
[16] Khan, A. T.; Khan, M. M.; Karthi, K. R. B. *Tetrahedron*. **2010**, 66, 7762.
[17] Clarke, P. A.; Zaytzev, P. A.; Whitwood, A. C. *Tetrahedron Lett*. **2007**, 48, 5209.
[18] Mishra, S.; Ghosh, R. *Tetrahedron Lett*. **2011**, 52, 2857.
[19] Wang, H.-J.; Mo, L.-P.; Zhang, Z.-H. *ACS Comb. Sci*. **2011**, 13, 181.
[20] Sajadikhah S. S.; Maghsoodlou M. T.; Hazeri N.; Habibi-khorassani S. M.; Shams-Najafi S. J.; *Monatsh Chem*, **2012**, 143, 939.
[21] Sajadikhah S. S.; Maghsoodlou M. T.; Hazeri N.; Habibi-khorassani S. M.; Willis A. C.; *Chin. Chem. Lett*, **2012**, 23, 569.
[22] Lashkari M.; Maghsoodlou M. T.; Hazeri N.; Habibi-khorassani S. M.; Sajadikhah S. S.; Doostmohamadi R.; *Synth. Commun*, **2013**, 43, 635.
[23] Ramachandran R.; Jayanthi S.; Jeong Y. T. *Tetrahedron*. 2012, 68, 363.
[24] Khandan-Barani, K.; Kangani, M.; Mirbalouchzehi, M.; Siroos, Z. *Inorganic, and Nano-Metal Chem*. **2017**, 47, 751.
[25] Maghsoodlou, M. T.; Khandan-Barani, K.; Hazeri, N.; Habibi-Khorassani, S.M.; Willis, A.C. *Res Chem Intermed*. **2014**, 40, 779.
[26] Maghsoodlou, M. T.; Hazeri, N.; Khandan-Barani, K.; Habibi-Korassani, S. M.; Abedi, A. *J. Hetercyclic Chem*. **2014**, 51, E152.
[27] Khandan-Barani, K. *Iran. J. Org. Chem*. **2018**, 10, 2489.