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One-pot five-component synthesis of highly functionalized piperidines using oxalic acid dihydrate as a homogenous catalyst

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Abstract

An efficient green protocol is described for the preparation of highly functionalized piperidines *via* a one-pot five-component reaction between aromatic aldehydes, anilines and β-ketoesters in the presence of oxalic acid dihydrate as catalyst in ethanol at ambient temperature. The structure as well as the relative stereochemistry of these compounds was confirmed by single X-ray crystallographic analysis.

Keywords: Piperidine; Heterocycle; Homogeneous catalyst; Oxalic acid dihydrate; Multi-component reaction

Piperidines and their analogues are important core structures in many biologically active natural products [1]. These compounds exhibit diverse biological activities such as antimalarial [2], anti-hypertensive [3], antibacterial [4], anticonvulsant and anti-inflammatory [5] α_1-AB antagonists [6], therapeutic agents in the treatment of influenza infection [7], cancer metastasis [8], diabetes [9], and also play important roles in many processes of disease treatments [10,11]. Recently, the synthesis of highly functionalized piperidines have been reported using multi-component reactions in the presence of L-proline/TFA [2], $InCl_3$ [12], bromodimethylsulfonium bromide (BDMS) [13], tetrabutylammonium tribromide (TBATB) [14], iodine [15], cerium ammonium nitrate (CAN) [16], $ZrOCl_2{\cdot}8H_2O$ [17], picric acid [18], and silica-supported boron trifluoride ($BF_3{\cdot}SiO_2$) [19] as catalyst. Owing to the importance of piperidines from a pharmaceutical and biological point of view, there is still the need to develop an efficient, mild and environmentally benign protocol for the synthesis of highly substituted piperidines.

On the contrary, the use of organic catalysts has received considerable attention in organic synthesis due to their important advantages, such as the possibility of performing reactions in the presence of acid-sensitive substrates, performing reactions in milder reaction conditions, and selectivity [20].

As a part of our current studies on the development of efficient multi-component reactions for the preparation of interesting bioactive molecules [21–24], especially piperidine synthesis [25], herein we present a simple and efficient method for synthesis of highly substituted piperidines *via* a one-pot five-component reaction between aromatic aldehydes, anilines and β-ketoesters in the presence of oxalic acid dihydrate in ethanol at ambient temperature (Scheme 1).

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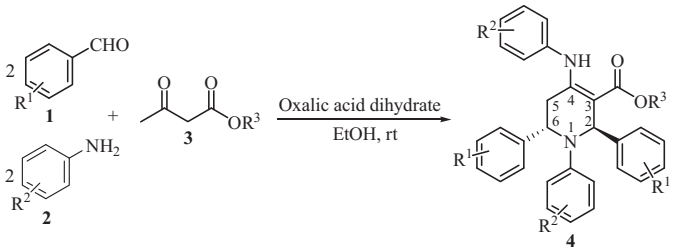


Scheme 1. Synthesis of highly substituted piperidines **4**.

In the initial experiment, the one-pot five-component reaction of 4-methyl benzaldehyde, aniline and ethyl acetoacetate was chosen as the model reaction to optimize the reaction conditions. It is noteworthy that no product was obtained in the absence of catalyst even after 24 h, which indicated that the catalyst's presence is necessary for this transformation. Also, the effect of different solvents and the effect of the amount of catalyst on the yield and rate of reaction were investigated. The best result was achieved in the presence of 0.09 g of catalyst in ethanol at ambient temperature. Under the optimized conditions, several reactions between different aromatic aldehydes, anilines, and methyl and/or ethyl acetoacetate were examined. The results are summarized in Table 1. The substituents on the benzene ring such as OMe, Me, F, Cl and Br were tolerated during the reaction. In all cases, the one-pot five-component reaction proceeded smoothly to afford the corresponding highly functionalized piperidines in good yields. The structures of compounds were deduced on the basis of IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. Also, the structure as well as the relative stereochemistry of piperidine **4**, for example, **4r**, was further confirmed by single X-ray crystallographic analysis (Fig. 1).

On the basis of the proposed mechanism in the literature [14–16,25], it is reasonable to assume that piperidine **4** results in initial condensation of aromatic aldehyde and β-ketoester **3** with aniline in the presence of oxalic acid dihydrate to give enamine **5** and imine **6**. Then, enamine **5** reacts with imine **6** to produce intermediate **7** through intermolecular Mannich-type reaction. The reaction between intermediate **7** and aldehyde gives intermediate **8**. Next, tautomerization of **8** generates intermediate **9**, which immediately undergoes intramolecular Mannich-type reaction to give intermediate **10**. Eventually, the intermediate **10** tautomerizes to generate the desired piperidine derivative **4** due to conjugation with the ester group (Scheme 2).

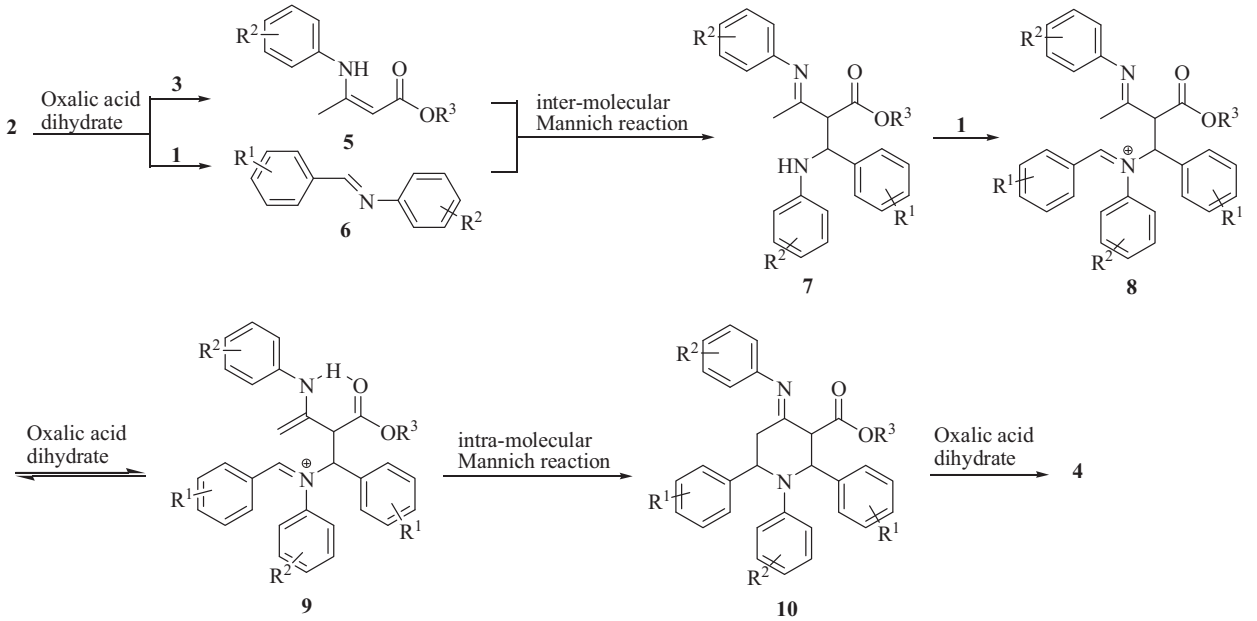
In conclusion, we have synthesized highly substituted piperidines *via* a one-pot five-component reaction between aromatic aldehydes, anilines and β-ketesters in ethanol using oxalic acid dihydrate as a catalyst at ambient

Table 1
Synthesis of highly substituted piperidines **4.**

Entry	R^1	R^2	R^3	Product	Time (h)	Yield (%)[a]	mp (°C)	Lit. mp (°C)[Ref,b]
1	4-Me	H	Et	**4a**	12	84	227–230	228–231 [15]
2	4-Me	H	Me	**4b**	12	81	214–216	215–217 [15]
3	4-F	H	Me	**4c**	10	84	202–204	205 [2]
4	3-Cl	H	Me	**4d**	12	78	218–220	220 [2]
5	4-Cl	H	Me	**4e**	10	80	185–186	189–191 [13]
6	4-OMe	H	Me	**4f**	16	67	178–181	180 [2]
7	H	H	Me	**4g**	12	78	190–192	194 [2]
8	H	4-Me	Me	**4h**	12	85	219–221	220–222 [17]
9	4-Cl	4-Me	Me	**4i**	10	83	217–219	213–215 [17]
10	3-Cl	4-Cl	Et	**4j**	12	82	190–192	190 [2]
11	4-Br	4-Cl	Me	**4k**	12	73	159–161	160–163 [2]
12	4-OMe	4-Cl	Me	**4l**	16	77	193–195	195 [2]
13	4-Me	4-Br	Me	**4m**	12	81	228–231	230–232 [15]
14	4-Me	4-Me	Me	**4n**	12	85	204–205	206–208 [15]
15	4-F	4-Cl	Me	**4o**	15	80	173–175	176 [2]
16	4-F	4-Me	Me	**4p**	12	84	200–202	200–202 [25]
17	4-Me	4-F	Et	**4q**	11	85	185–186	183–185 [25]
18	4-Me	4-Me	Et	**4r**	12	84	169–171	–
19	H	4-Br	Et	**4s**	12	82	196–198	–

[a] Isolated yield.
[b] All known products have been reported previously in the literature and were characterized by comparison of IR and NMR spectra with authentic samples.

Fig. 1. ORTEP representation of the X-ray structure of piperidine **4r**.



Scheme 2. Proposed reaction mechanism for synthesis of highly substituted piperidines **4**.

temperature. The present procedure offered several advantages such as mild and green reaction conditions, simplicity in operation, inexpensive catalyst, and good to high yields, which makes it a useful and attractive process for synthesis of these important compounds.

*1 General procedure for synthesis of highly substituted piperidine **4***

Initially, 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 oxalic acid dihydrate (0.09 g) at ambient temperature. Then, the aromatic aldehyde (2 mmol) was added and the reaction mixture was allowed to stir for appropriate time (Table 1). The progress of the reaction was monitored by TLC. After completion of the reaction, the tick precipitate was filtered off and washed with ethanol (3 × 2 mL) to give the pure product. Physical and chemical data of unknown products are presented below.!

*1.1 Ethyl 4-(p-tolylamino)-1,2,5,6-tetrahydro-1,2,6-trip-tolylpyridine-3-carboxylate (**4r**)*

White solid; mp 169–171 °C; IR (KBr) (υ_{max}/cm^{-1}): 3256 (NH), 1656 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.49 (t, 3H, J = 7.0 Hz, OCH_2CH_3), 2.20 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.78 (dd, 1H,

J = 15.1, 2.4 Hz, H′-5), 2.87 (dd, 1H, J = 15.1, 5.6 Hz, H″-5), 4.37 (dq, 1H, J = 10.4, 7.2 Hz, OCH_aH_b), 4.48 (dq, 1H, J = 10.4, 6.8 Hz, OCH_aH_b), 5.13 (d, 1H, J = 3.6 Hz, H-6), 6.23 (d, 2H, J = 8.4 Hz, ArH), 6.42 (s, 1H, H-2), 6.49 (d, 2H, J = 8.8 Hz, ArH), 6.89 (d, 2H, J = 10.8 Hz, ArH), 6.93 (d, 2H, J = 7.6 Hz, ArH), 7.08–7.29 (m, 8H, ArH), 10.26 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.8 (OCH_2CH_3), 20.1 (CH_3), 20.9 (CH_3), 21.0 (CH_3), 21.1 (CH_3), 33.6 (C-5), 55.0 (C-2), 57.9 (C-6), 59.5 (OCH_2CH_3), 97.8 (C-3), 112.8, 124.8, 125.9, 126.4, 126.6, 128.9, 129.2, 129.3, 129.4, 135.4, 135.6, 136.4, 140.0, 141.4, 145.0, 156.4 (C-4), 168.3 (C=O); MS (EI, 70 eV) m/z (%): 530 (M^+, 11), 457 (3), 439 (24), 320 (32), 208 (68), 115 (34), 91 (100), 77 (15), 55 (23%); anal. calcd. for $C_{36}H_{38}N_2O_2$: C 81.47; H 7.22, N, 5.28; found: C 81.61, H 7.29, N 5.35. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 851584 for **4r**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk), or *via* www.ccdc.cam.ac.uk/data request/cif.

*1.2 Ethyl 4-(4-bromophenylamino)-1-(4-bromophenyl)-1,2,5,6-tetrahydro-2,6-diphenylpyridine-3-carboxylate (**4s**)*

White solid; mp 196–198 °C; IR (KBr) (υ_{max}/cm^{-1}): 3248 (NH), 1648 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50 (t, 3H, J = 6.8 Hz, OCH_2CH_3), 2.74 (d, 1H, J = 15.2 Hz, H′-5), 2. 89 (dd 1H, J = 15.2, 5.6 Hz, H″-5), 4.35–4.40 (m, 1H, OCH_aH_b), 4.46–4.52 (m, 1H, OCH_aH_b), 5.13 (d, 1H, J = 4.0 Hz, H-6), 6.14 (d, 2H, J = 8.0 Hz, ArH), 6.41 (s, 1H, H-2), 6.42 (d, 2H, J = 8.0 Hz, ArH), 7.14–7.34 (m, 14H, ArH), 10.26 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.8 (OCH_2CH_3), 33.4 (C-5), 55.2 (C-2), 58.3 (C-6), 59.9 (OCH_2CH_3), 98.8 (C-3), 108.4, 114.6, 119.1, 126.3, 126.5, 126.6, 127.2, 127.5, 128.4, 128.8, 131.6, 132.0, 136.9, 142.1, 143.2, 145.9, 155.2 (C-4), 168.1 (C=O); MS (EI, 70 eV) m/z (%): 634 (M + 2, 5), 632 (M^+, 3), 555 (19), 447 (100), 324 (58), 296 (26), 278 (28), 252 (44), 115 (40), 91 (51), 77 (33), 55 (66); anal. calcd. for $C_{32}H_{28}Br_2N_2O_2$: C 60.78; H 4.46, N, 4.43; found: C 61.04, H 4.57, N 4.47.

Acknowledgments

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