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One-pot multi-component green synthesis of highly substituted piperidines

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An effective and expeditious method of the synthesis of a highly functionalized piperidines, catalyzed by nontoxic, recyclable and environment friendly sodium lauryl sulfate (SLS), *via* one-pot multi-component condensation of aldehydes, amines and β-ketoesters in water at room temperature, has been developed. This new protocol has advantages such as moderate to high yields of products obtained after simple post reaction workup. Structure of the synthesized compounds **4a–4j** have been elucidated based on the ^{1}H NMR, ^{13}C NMR, FT-IR spectroscopy and elemental analysis.

1. Introduction

Heterocyclic compounds containing nitrogen atom are wide spread in nature and have significant practical importance because of their applications in medicine and agriculture.[1,2] They are also used as functional materials. The development of new and efficient methods for the synthesis of *N*-heterocycles is one of the greater interests of modern synthetic organic chemistry.[3-5]

Synthesis of complex heterocyclic molecules can be easily achieved starting from readily available starting materials in a single step multi-component reactions (MCRs).[6] In most of the cases these reactions are advantageous over the linear step-wise syntheses because of the operational simplicity, shorter reaction time, ecological concerns, low processing costs and avoidance of protection and deprotection processes.[7]

Substituted piperidines are widely present in naturally occurring and synthetic drugs.[8] A variety of structural features are exhibited by synthetically prepared piperidines including many significant biological activities. Many methods have been extensively studied for the synthesis of piperidines because of their antihistamic,[9] anti-HIV,[10] anticancer,[11] antimicrobial,[12] anti-malarial,[13] anti-inflammatory,[14] insecticidal[15] and other biological activities.

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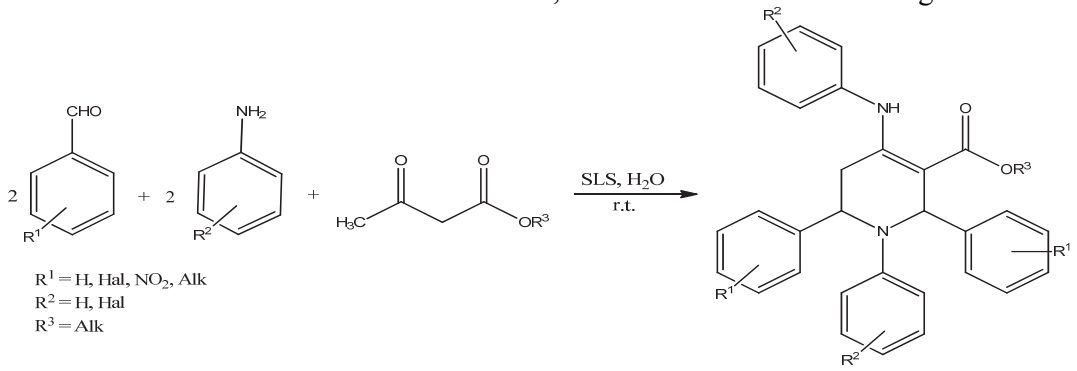
Recently, many MCRs have been reported for the syntheses of piperidine derivatives in the presence of L-proline/tetrahydrofuran (THF),[13] indiumtrichloride ($InCl_3$),[16] bromodimethyl sulfoniumbromide (BDMS),[17] tetrabutylammoniumtribromide (TBATB),[18] iodine,[19] cerium ammoniumnitrate (CAN),[20] $ZrOCl_2{\cdot}8H_2O$,[21] citric acid,[22] calix[*n*]arenes,[23] tris(pentafluorophenyl)borane [$B(C_6F_5)_3$],[24] sulfamic acid[25] and 2,6-pyridinedicarboxylic acid[26] used as catalysts. Some of these methods are having such draw backs as long reaction times, unsatisfactory yields or use of expensive catalysts. All these prompted us to develop a new simple and greener method of the synthesis of piperidines.

In the present communication we have reported a simple and efficient procedure of one-pot multi-component synthesis of highly substituted piperidines by the reaction between aromatic aldehydes, anilines and β-ketoesters in the presence of SLS, used as a catalyst, under mild reaction conditions at room temperature (Scheme 1). SLS is cheap, readily available, versatile, environment friendly and recyclable. The reactions have been carried out in water, what eliminated the use of organic solvents.



Scheme 1. One-pot multi-componet synthesis of substituted piperidines

2. Results and Discussion

Initially benzaldehyde (2 mmol) was treated with aniline (2 mmol) and ethyl acetoacetate (1 mmol) with water in absence of catalyst. No product was obtained at room temperature after 24 h (Table 1, entry 8). To determine the best experimental conditions, the reaction was carried out in the presence of 0.02 g SLS in water at 100 ^{0}C. The reaction proceeded smoothly to give the corresponding functionalized piperidine in 30% yield after 24 h (Table 1, entry 13). When the same reaction was carried out under solvent-free conditions, the product was obtained 25% yield after 24 h (Table 1, entry 14). The best results were obtained in the presence of 0.02 g SLS in water at room temperature (Table 1, entry 9).

Table 1. Condensation of benzaldehyde, aniline and ethylacetoacetate in different conditions.

Entry	Catalyst	Solvent	Time, h	T, ^{0}C	Yield, %
1	$NiCl_2$	Water	24	50	40
2	ZnO	Ethanol	24	80	No product
3	Fe_2O_3	Ethanol	24	70	No product
4	CaO	Ethanol	8	80	No product
5	L-Proline	Ethanol	10	80	40
6	CuO	Ethanol	14	60	No product
7	Al_2O_3	Ethanol	10	50	No product
8	Without catalyst	Water	24	r.t.	No product
9	SLS	Water	6	r.t.	95
10	Twine-20	Water	10	50	No product
11	Cetrimide	Water	10	r.t.	No product
12	Triton X-100	Water	10	r.t.	No product
13	SLS	Water	24	100	30
14	SLS	Without Solvent	24	r.t.	25

Conditions: benzaldehyde (2 mmol), aniline (2 mmol), ethyl acetoacetate (1 mmol), solvent (10 mL), catalyst (0.02 g).

Several substituted benzaldehydes, anilines, methyl/ethyl acetoacetates (EAA) were examined under the optimized reaction conditions. Benzaldehydes with EWG (electron withdrawing) groups underwent the reaction with anilines efficiently to give the corresponding piperidines in moderate to high yields. Aldehydes possessing the EDG groups *e.g.* -CH_3 were less reactive (Table 2, entry 9).

Table 2. Synthesis of substituted piperidines.

Entry	R^1	R^2	R^3	Product	Time, h	Yield, %	M.p., ^{0}C
1	H	H	Et	**4a**	6	90	174
2	H	4-Cl	Et	**4b**	6	85	220
3	2-F	H	Et	**4c**	7	65	128
4	4-Cl	H	Et	**4d**	6	95	215
5	4-NO_2	H	Me	**4e**	6	80	236
6	3-NO_2	H	Et	**4f**	7	80	247
7	4-F	H	Et	**4g**	6	80	170
8	H	4-F	Et	**4h**	7	80	144
9	4-Me	4-Cl	Et	**4L**	8	75	234
10	4-OH	H	Et	**4j**	6	90	233

Conditions: aromatic aldehyde (2 mmol) aromatic amine (2 mmol), β-ketoester (1 mmol), SLS (0.02 g), water (10 mL), room temperatue.

The structures of newly synthesized compounds **4a-4j** has been confirmed based on the 1H NMR, ^{13}C NMR and FT-IR spectroscopic and elemental analysis data.

The temperature seems does not have any significant effect on the products yield. The yields of the products did not also improved when the amount of SLS was increased. The results are presented in Table 3.

Table 3. Effect of SLS loading on the synthesis of piperidine **4a** at room temperature.

Entry	SLS, g	Time, h	Yield, %
1	0.005	6	20
2	0.01	6	30
3	0.02	6	95
4	0.05	6	30
5	0.10	6	No product

Conditions: benzaldehyde (2 mmol), aniline (2 mmol), ethyl acetoacetate (1 mmol), SLS (0.02 g), water (10 mL), room temperature.

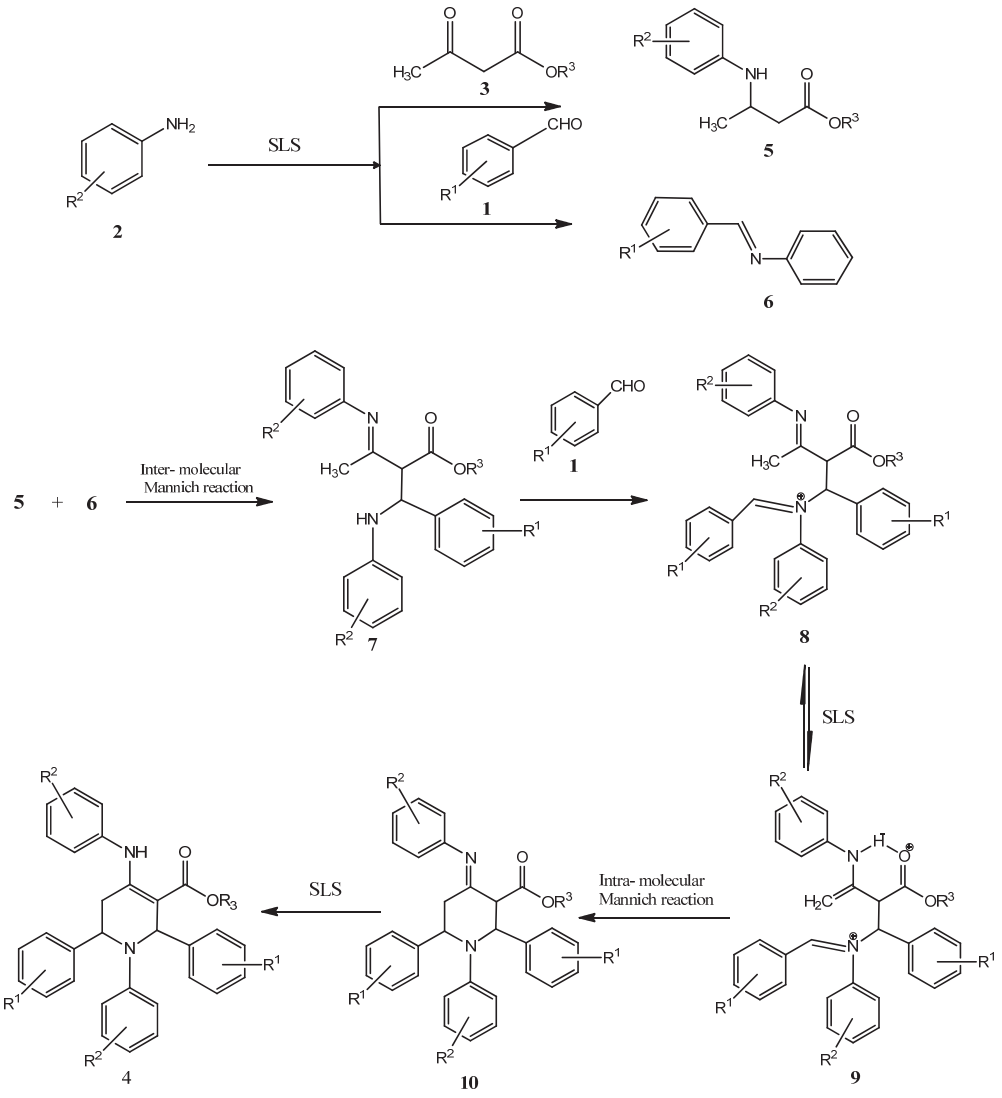
Based on previous literature records,[13, 16-23] it is reasonable to assume following mechanism of the reaction. Piperidines **4** results from initial condensation of aromatic aldehydes (**1**) and β-ketoesters (3) with anilines (**2**), in the presence of SLS, to give enamine **5** and imine **6** (Scheme 2) which undergone intermolecular Mannich-type reaction to produce intermediate **7**. The reaction between intermediate **7** and **1** gives intermediate **8** by the elimination of H_2O. Tautomerization of **8** generates intermediate **9**, which immediately undergoes intra-molecular Mannich-type reaction to give intermediate **10**. Finally, the **10** tautomerizes to generate the desired piperidines derivative **4** owing to conjugation with the ester group.

This reaction can be regarded as an efficient approach for the preparation of synthetically and pharmaceuptically important piperidine systems.

3. Conclusions

A general methodology of the formation of highly functionalized piperidines from commonly available starting materials, in presence of catalytic amounts of sodiumlaurylsulfate, *via* one-pot three component reaction is reported. The salient features of this protocol are good yields, mild reaction conditions, environment friendly, superior atom economy and the readily accessibility of the catalyst.

In addition, we proposed the possibility for the formation of piperidines *via* double Mannich-type intermediates.



Scheme 2. Proposed molecular mechanism

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4. Experimental

4.1. Materials and Methods

All the chemicals were received commercially and used without further purification. Melting points were determined in melting point apparatus, using open capillary tube and are uncorrected. NMR spectra were recorded with a Bruker AV III spectrometer at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR) using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as internal standard. FT-IR spectra of

compounds were recorded using KBr pellets on Shimadzu IR Affinity-1, Fourier-Transform infrared spectrometer.

4.2. General procedure

A mixture of aromatic amine **2** (2 mmol) and β-ketoester **3** (1 mmol) in 10 ml water was stirred for 20 min in the presence of 0.02 g sodiumlaurylsulfate at room temperature. Next the aromatic aldehyde **1** (2 mmol) was added and the reaction mixture was stirred for the time indicated in Table 2. The progress of reactions was monitored by thin layer chromatography (TLC), eluted with ethyl acetate and n-hexane (3:7) mixture. After completion of the reaction, a thick precipitate was filtered off and washed with water. The crystalline pure products were obtained by further recrystalization from ethanol.

4.3 Physical and Spectral Data

Ethyl-1,2,6-triphenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4a)
Yield = 90, White yellow solid, melting point = 174 ^{0}C, **Elemental Analysis Data** found (required %) C = 80.85 (80.98), H = 6.30 (6.37), N = 5.80 (5.90), O = 6.68 (6.74). **FT-IR** (KBr): 3244.27 (N-H), 1651.07 (C=O), 1581.63 (C=C) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) ppm: 1.19 (t, *J* = 7.2, 6.8 Hz, 3H), 1.41 (dd, *J* = 2, 15.2 Hz, 1H), 2.79 (dd, *J* = 6, 5.6, 15 Hz, 1H), 4.09-4.26 (m, 1H), 4.28-4.38 (m, 1H), 5.07 (d, *J* = 4Hz, 1H), 6.12-6.21 (m, 2H), 6.99 (s, 1H), 7. (d, *J* = 8.4 Hz, 2H), 7.02 (t, *J* = 7.2 Hz, 1H), 7.05-7.10 (m, 5H), 7.12-7.18 (m, 2H), 7.20-7.25 (m, 6H), 7.58 (d, *J* = 7.6 Hz, 2H), 10.21 (s, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) ppm: 14.9, 33.7, 55.2, 58.3, 59.8, 98.3, 113.0, 116.2, 125.8, 125.9, 126.4, 126.5, 126.7, 127.2, 128.3, 128.7, 128.9, 128.9, 137.9, 142.9, 144.1, 147.0, 156.2, 168.3.

Ethyl-1-(4-chlorophenyl)-4(4chlorophenyl)amino),2,6-diphenyl-1,2,5,6-tertahydropyridine-3-carboxylate (4b)

Yield = 85, Yellow solid, melting point = 220 ^{0}C, **Elemental Analysis Data** found (required %) C = 70.62 (70.72), H = 5.10 (5.19), Cl = 12.95 (13.05), N = 5.10 (5.15), O = 5.80 (5.89). **FT-IR** (KBr): 3246.20 (N-H), 1645.28 (C=O), 1492.90 (C=C) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) ppm: 1.52-1.49 (t, *J* = 6.0 Hz, 3H), 2.75-2.72 (d, *J* = 12.0 Hz, 1H), 2.91-2.87 (dd, *J* = 24.0, 4.0 Hz, 1H), 4.39- 4.35 (m, 1H), 4.52-4.49 (m, 1H), 5.14-5.13 (s, 1H), 6.21-6.19 (d, *J* = 8.0 Hz, 2H), 6.43 (s, 1H), 6.48-6.46 (d, *J* = 8.0 Hz, 2H), 7.04-7.02 (d, *J* = 8.0 Hz, 2H), 7.09-7.07 (d, *J* = 8.0 Hz, 2H), 7.19-7.17 (d, *J* = 8.0 Hz, 2H), 7.31-7.27 (m, 8H), 10.26 (br s, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) ppm: 14.8, 33.5, 55.3, 58.3, 59.9, 98.7, 114.0, 121.2, 126.3, 126.5, 126.6, 127.0, 127.5, 128.4, 128.7, 128.8, 129.0, 131.4, 136.4, 142.3, 143.3, 145.5, 155.4, 168.1.

Ethyl-2,6-bis(4-chlorophenyl)-1,2,5,6-tetrahydro-1-phenyl-4-(phenylamino)pyridine-3-carboxylate (4d)

Yield = 95, White solid, melting point = 215 ^{0}C, **Elemental Analysis Data** found (required %) C = 70.65 (70.72), H = 5.15 (5.19), Cl = 12.95 (13.05), N = 5.08 (5.15), O = 5.80 (5.89). **FT-IR** (KBr): 3057.17 (N-H), 1649.14 (C=O), 1485 (C=C) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) ppm: 1.47-1.43 (t, *J* = 12.0 Hz, 3H), 2.76-2.72 (d, *J* = 16.0 Hz, 1H), 2.85-2.80 (dd, *J* = 32.0, 4.0 Hz, 1H), 4.36- 4.28 (m, 1H), 4.48-4.40 (m, 1H), 5.09 (s, 1H), 6.36 (s, 1H), 6.41-6.39 (d, *J* = 8.0 Hz, 2H), 6.46-6.44 (d, *J* = 8.0 Hz, 2H), 6.66-6.62 (t, *J* = 8.0 Hz, 1H), 7.17-7,04 (m, 7H), 7.27-7.22 (m, 6H), 10.31 (br s, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) ppm: 14.8, 33.7, 54.7, 57.4, 59.9, 97.8, 112.9, 116.7, 125.7, 125.9, 127.8, 128.0, 128.4, 128.8, 129.0, 129.1, 132.1, 132.9, 137.7, 140.9, 142.5, 146.5, 155.8, 167.9.

Methyl-1,2,5,6-tetrahydro-2,6-bis(4-nitrophenyl)-1-phenyl-4-(phenylamino)pyridine-3-carboxylate (4e)

Yield = 80, Yellow solid, melting point = 236 ^{0}C, **Elemental Analysis Data** found (required %) C = 67.58 (67.63), H = 4.70 (4.76), N = 10.10 (10.18), O = 17.40 (17.44). **FT-IR** (KBr): 3239 (N-H), 1667 (C=O), 1530 (C=C) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) ppm: 2.87 (s, 2H), 3.97 (s, 3H), 5.27 (s, 1H), 6.44-6.39 (t, *J* = 10.0 Hz, 3H), 6.48 (s, 1H), 6.71-6.68 (t, *J* = 6.0 Hz, 1H), 7.13-7.04 (t, *J* = 18.0 Hz, 2H), 7.16 (s, 3H), 7.30-7.26 (m, 2H), 7.51- 7.49 (d, *J* = 8.0 Hz, 2H), 8.17-8.12 (t, *J* = 10.0 Hz, 5H), 10.28 (br s, 1H, NH). **^{13}C NMR** (100 MHz, $CDCl_3$) ppm: 25.6, 33.6, 51.5, 55.2, 57.3, 67.9, 96.7, 112.9, 117.7, 123.7, 123.8, 123.9, 124.0, 125.5, 126.5, 127.4, 127.4, 127.6, 127.8, 129.1, 129.2, 129.4, 137.1, 145.8, 146.8, 147.3, 149.8, 151.6, 155.5, 167.9.

Ethyl-1,2,5,6-tetrahydro-2,6-bis(3-nitrophenyl)-1-phenyl-4-(phenylamino)pyridine-3-carboxylate (4f)

Yield = 80, Yellow solid, melting point = 247 ^{0}C, **Elemental Analysis Data** found (required %) C = 68.00 (68.07), H = 4.95 (5.00), N = 9.87 (9.92), O = 16.94 (17.00). **FT-IR** (KBr): 3233 (N-H), 1659 (C=O), 1504 (C=C) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) ppm: 1.57-1.54 (t, *J* = 6.0 Hz, 3H), 2.92-2.92 (s, 2H), 4.41- 4.37 (m, 1H), 4.59-4.55 (m, 1H), 5.36 (s, 1H), 6.44-6.42 (m, 2H), 6.48-6.46 (d, *J* = 8.0 Hz, 2H), 6.52 (s, 1H), 6.74-6.71 (t, *J* = 6.0 Hz, 1H), 7.19-7.11 (m, 5H), 7.51-7.46 (m, 3H), 7.68-7.66 (d, *J* = 8.0Hz, 1H), 7.98 (s, 1H), 8.17-8.12 (m, 2H), 8.35 (s, 1H), 10.38 (br s, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) ppm: 14.8, 25.6, 33.8, 55.2, 57.0, 60.3, 67.9, 97.0, 113.1, 117.7, 121.4,121.7, 121.8, 122.5, 125.6, 126.5, 129.1, 129.3, 129.4, 129.7, 132.3, 132.6, 137.2, 144.5, 145.8, 146.4, 148.6, 148.7, 155.3, 167.7.

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