

SbCl₃ as an Efficient Catalyst for the One-pot Synthesis of Highly Substituted Piperidines

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Highly substituted piperidines were synthesized *via* condensation of aromatic aldehydes and aromatic amines with β -ketoesters in the presence of antimony(III) chloride at the ambient condition. This reaction has any advantages such as easy work-up, clean procedure, and good yields.

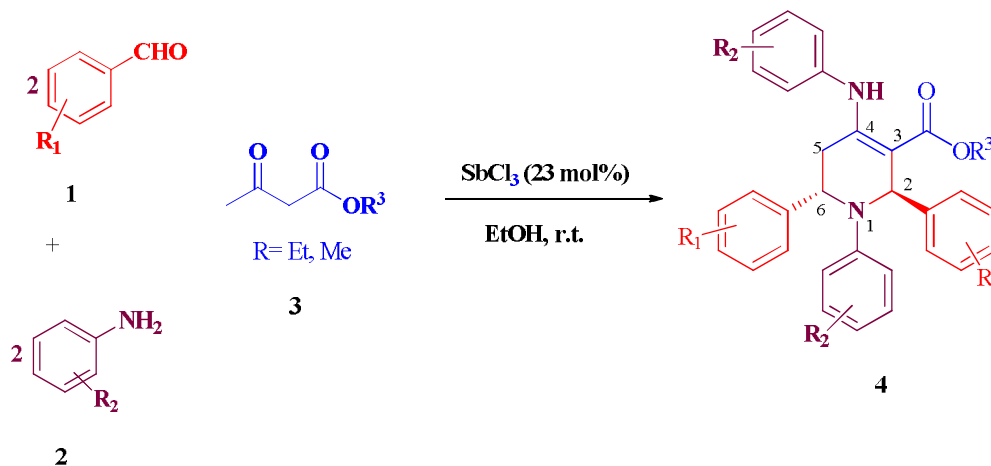
Keywords: Antimony trichloride, Piperidines, Good yields, Ambient condition

INTRODUCTION

Multi-component reactions (MCRs) have an important role in medicinal and organic chemistry for their high degree of atom economy and applications in combinatorial chemistry [1]. They have inherent advantages over two-component reactions in several aspects: the simplicity of a one-pot procedure, possible structure variations, complicated synthesis and a large number of accessible compounds [2]. Nevertheless, continued efforts are being made to explore new MCRs for developing popular organic reactions [3]. The highly functionalized piperidines are widely distributed in many natural products, biologically active molecules and organic fine chemicals [4-6]. Compounds containing the piperidine structural motif exhibit antihypertensive [7], anti-bacterial [8], anticonvulsant, and anti-inflammatory activities [9]. They are also involved in a mono-amino oxidase (MAO)-based mechanism in Parkinson's disease [10-12], and as inhibitors of farnesyl transferase [13] and dihydroborate dehydrogenase [14]. Piperidine scaffolds are also important as a part of the active ingredient in a number of commercially available drugs [15-18], such as Donepezil

used for the treatment of Alzheimer's disease, Naratriptan (used for the treatment of migraine headaches), Sertindole and Risperidone (both used for the treatment of schizophrenia). Thus, enormous uses of this scaffold have prompted significant efforts towards the synthesis of functionalized piperidines. For the aforementioned purposes, various conventional multistep and low yielding methods have been reported in the literature, such as intramolecular Michael reaction [19], imino Diels-Alder reactions [20,21], tandem cyclopropane ring opening/Conia-ene cyclizations [22], intramolecular Mannich reactions onto iminium ions [23], and aza-Prins-cyclization [24-26]. A few one-pot syntheses of functionalized piperidines using MCR strategy have been reported such as a bromodimethylsulfonium bromide (BDMS) [27], tetrabutylammonium tribromide (TBATB) [28], combination of L-proline/TFA [29], InCl₃ [30], picric acid [31], PEG-embedded KBr₃ [32], ZrOCl₂·8H₂O [33], ZrCl₄ [34], CAN [35], Bi(NO₃)₃·5H₂O [36], FeCl₃/SiO₂ NPs [37], BF₃/SiO₂ [38] and chiral phosphoric acids [39,40]. However, some of these catalysts suffer from some drawbacks such as prolonged reaction times, low yields, toxicity and recovery of the catalyst and using expensive and hazardous solvents. Therefore, introducing clean processes and utilizing efficient catalysts which can be simply worked-up at the end

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Scheme 1. Synthesis of highly substituted piperidines in the presence of SbCl_3 at room temperature

of reactions have been under permanent attention. In continue of our research on the synthesis of piperidines [41-44], herein, we report an efficient synthesis of these compounds in the presence of SbCl_3 as the catalyst at room temperature (Scheme 1).

EXPERIMENTAL

Melting points and IR spectra of all compounds were measured on an Electrothermal 9100 apparatus and a JASCO FTIR 460 Plus spectrometer, respectively. The ^1H NMR spectra were obtained on Bruker DRX-400 Avance instruments with CDCl_3 as a solvent. All reagents and solvents obtained from Fluka, Merck and were used without further purification.

Typical Procedure for the Synthesis of Highly Substituted Piperidines

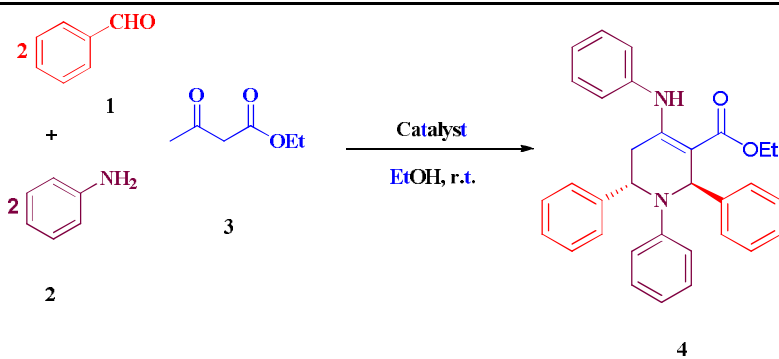
First, a solution of aromatic amine **2** (2 mmol) and β -ketoester **3** (1 mmol) in EtOH (5 ml) was stirred for 20 min in the presence of SbCl_3 (23 mol%) at ambient temperature. Next, the aromatic aldehyde **1** (2 mmol) was added and the reaction mixture was allowed to stir for the appropriate time. After completion of the reaction as monitored by TLC, the obtained solid was filtered and just washed with cold EtOH (3×2 ml) to remove the catalyst and give the pure

product **4**.

Selected Spectroscopic Data of some Products are Given Below

Ethyl-1-phenyl-4-(phenylamino)-2,6-di-p-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylate (4b). White solid; m.p.: 227-229 °C. FT-IR (KBr): 3244 (NH), 1649 ($\text{C}=\text{O}$) cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz) δ : 1.51 (t, 3H, $J=7.0$ Hz, OCH_2CH_3), 2.37 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.81 (dd, 1H, $J=15.2, 2.0$ Hz, H'-5), 2.91 (dd, 1H, $J=15.2, 5.6$ Hz, H''-5), 4.34-4.46 (m, 1H, OCH_2H_3), 4.48-4.52 (m, 1H, OCH_2H_3), 5.16 (d, 1H, $J=3.6$ Hz, H-6), 6.34 (d, 2H, $J=6.0$ Hz, ArH), 6.36 (s, 1H, H-2), 6.58 (d, 2H, $J=8.4$ Hz, ArH), 6.64 (t, 1H, $J=7.2$ Hz, ArH), 7.09-7.29 (m, 13H, ArH), 10.35 (s, 1H, NH).

Ethyl-2,6-bis(4-methoxyphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4d). White solid; m.p.: 166-167 °C. FT-IR (KBr): 3235 (NH), 1669 ($\text{C}=\text{O}$) cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz) δ : 1.50 (t, 3H, $J=7.2$ Hz, OCH_2CH_3), 2.80 (dd, 1H, $J=15.2, 2.4$ Hz, H'-5), 2.90 (dd, 1H, $J=15.2, 5.6$ Hz, H''-5), 3.82 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.38 (dq, 1H, $J=10.8, 7.2$ Hz, OCH_2CH_3), 4.50 (dq, 1H, $J=10.8, 7.0$ Hz, OCH_2CH_3), 5.13 (d, 1H, $J=2.8$ Hz, H-6), 6.41 (d, 2H, $J=6.8$ Hz, ArH), 6.42 (s, 1H, H-2), 6.58 (d, 2H, $J=8.4$ Hz, ArH), 6.65 (t, 1H, $J=7.2$ Hz, ArH), 6.84-6.87 (m, 4H, ArH), 7.09-7.29 (m, 9H, ArH), 10.36 (s, 1H, NH).

Table 1. Different Catalytic Systems and Catalytic Activity Evaluation for the Synthesis of Highly Substituted Piperidines


Entry	Catalyst	Solvent	Time (h)	Isolated yields (%)
1	-	EtOH	48	-
2	RbCl (20 mol%)	EtOH	24	-
3	NdCl ₃ ·6H ₂ O (20 mol%)	EtOH	24	33
4	CeCl ₃ ·7H ₂ O (20 mol%)	EtOH	24	47
5	SbCl ₃ (20 mol%)	EtOH	8	68
6	SbCl ₃ (23 mol%)	EtOH	8	84
7	SbCl ₃ (25 mol%)	EtOH	8	84
8	SbCl ₃ (23 mol%)	MeOH	24	46
9	SbCl ₃ (23 mol%)	CH ₃ CN	24	45

RESULTS AND DISCUSSION

We have performed a set of preliminary experiments on benzaldehyde, aniline and ethylacetoacetate in the presence of 20 mol% catalyst as a model reaction. The results are shown in Table 1. In the initial inspection, different Lewis acids were screened as the catalyst in the model reaction (Table 1, entries 2-5). As seen in Table 1, the reaction did not progress even after 48 h without catalyst. Moreover, we tested this reaction at ambient condition to introduce a neat procedure.

Under the optimized reaction conditions, the generality

of the reaction was investigated using various aldehydes, anilines and β -ketoesters to produce piperidines derivatives. The results are summarized in Table 2. These results indicate the effectiveness of electron-withdrawing and electron-donating groups on the time and yield of the reaction. Benzaldehydes with electron-withdrawing groups react with aniline better than electron-donating groups and this observation could be attributed to the resonance effect. In our research work, aliphatic aldehyde and amine such as propanal and 1-butylamin did not tolerate the reaction.

According to the literature [43-44], a mechanism was suggested for this transformation (Scheme 2). First, β -

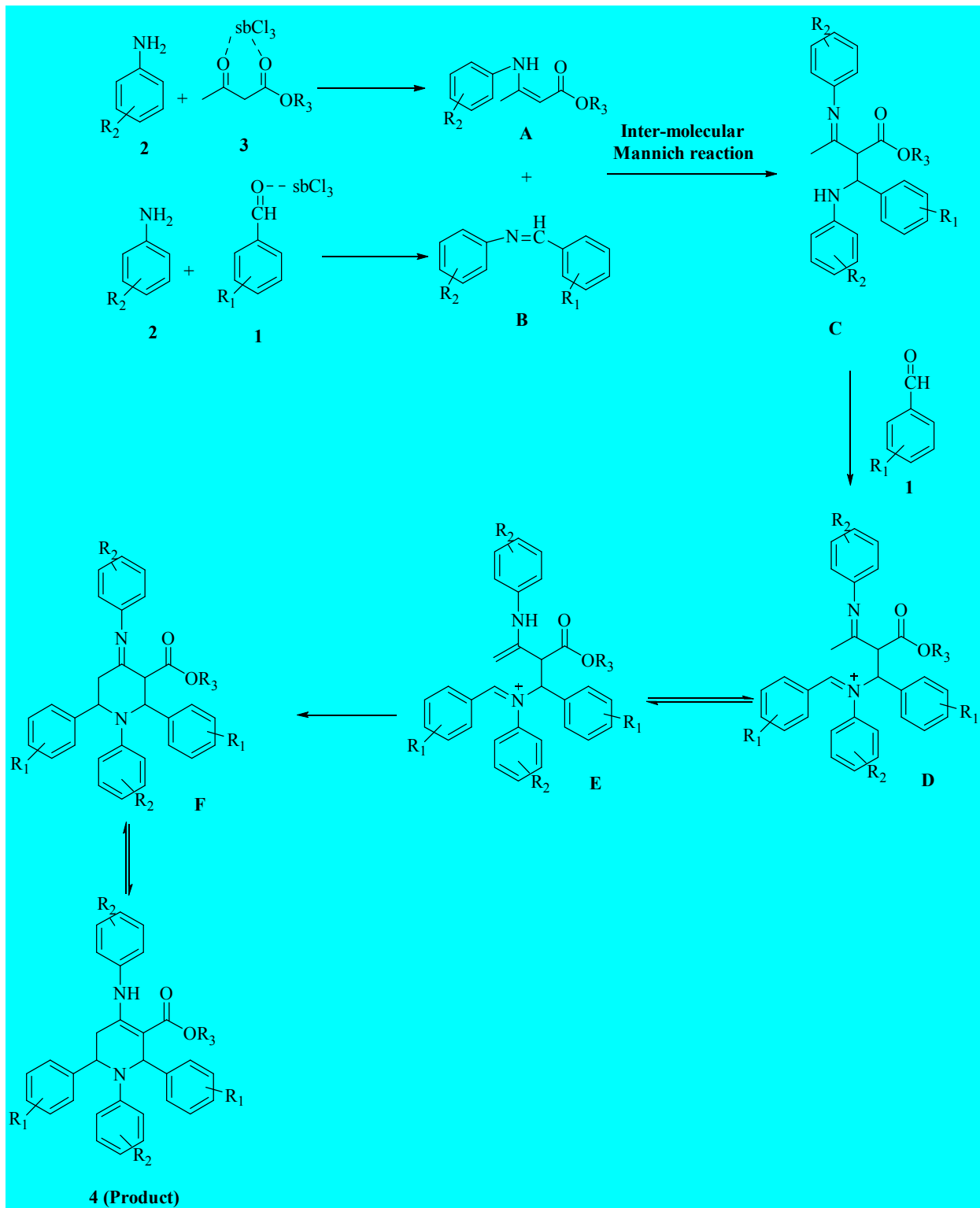
Table 2. Synthesis of Highly Substituted Piperidines

Entry	Product	R ¹	R ²	R ³	Time (h)	Isolated yield (%)	m.p. (lit. reported) [41-44]
1	4a	4-Me	H	Me	6	78	215-216 (215-217)
2	4b	4-Me	H	Et	6	85	227-229 (228-231)
3	4c	4-OMe	H	Me	9	75	186-188 (187-188)
4	4d	4-OMe	H	Et	5	44	166-167 (166-168)
5	4e	4-Cl	H	Me	11	95	188-190 (189-191)
6	4f	H	H	Me	7	82	169-171 (169-171)
7	4g	H	H	Et	8	84	172-174 (174-175)
8	4h	H	4-OMe	Et	9	60	178-180 (179-181)
9	4i	H	4-Cl	Et	13	76	197-200 (197-198)
10	4j	4-OMe	4-Cl	Me	6	72	192-195 (194-195)
11	4k	4-Me	4-Br	Me	10	68	229-231 (230-232)
12	4l	4-Me	4-F	Et	17	54	184-186 (183-185)
13	4m	4-Me	3,4-di-Cl	Et	17	56	185-187 (173-175)
14	4n	H	4-Br	Et	8	81	197-199 (196-198)
15	4o	4-OMe	4-Br	Me	5	77	175-177 (178)
16	4p	4-NO ₂	4-OMe	Me	4	99	198-200 (198-199)
17	4q	3-Br	4-Ome	Et	9	83	191-200 (198-200)
18	4r	4-F	4-Cl	Me	9	72	173-175 (174-175)
19	4s	4-Br	4-Cl	Me	11	58	170-172 (160-162)
20	4t	4-F	H	Me	9	92	192-194 (193-195)

ketoesters 3 and aldehyde 1 react with aniline 2 in the presence of SbCl₃ to give enamine A and imine B, respectively. Next, the reaction between enamine A and imine B leads to intermediate C through intermolecular Mannich-type reaction. The intermediate C reacts with aldehyde 1 to generate intermediate D. Then, tautomerization of D generates intermediate E, which

immediately undergoes intramolecular Mannich-type reaction to produce intermediate F. In the final step, tautomerization of the intermediate F generates the desired piperidine 4 due to conjugation with the ester group.

To show the merit of the present work in comparison with the reported results in the literature, we compared the result of SbCl₃ with some catalysts reported in the



Scheme 2. Proposed mechanism for the synthesis of highly substituted piperidines

Table 3. Comparison of SbCl₃ with other Reported Catalyst

Entry	Product	Catalyst/Condition	Time (h)	Yield (%)	[Ref.]
1	4g	ZrCl ₄ /EtOH, r.t	15	91	[34]
2	4g	Bi(NO ₃) ₃ .5H ₂ O/EtOH, r.t	16	79	[36]
4	4g	SbCl ₃ /EtOH, r.t	8	84	Present work
3	4f	BF ₃ .SiO ₂ /MeOH, 65 °C	9	78	[38]
4	4f	SbCl ₃ /EtOH, r.t	7	82	Present work

literature. It was found that SbCl₃ is a more efficient catalyst in comparison with some other reported catalysts (Table 3).

CONCLUSIONS

In summary, antimony(III) chloride is a cost-effective and highly efficient Lewis acid catalyst for the synthesis of highly substituted piperidines. The advantages of this procedure are: mild reaction conditions, cleaner reaction profiles, improved yields, and simplicity of the operation. The highly catalytic nature of antimony(III) chloride and its wide applicability should make this protocol an attractive alternative for the existing methods.

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