Bi(OTf)₃ as a powerful and efficient catalyst for the synthesis of highly functionalized piperidines

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ABSTRACT

A simple, and efficient multicomponent synthesis of a highly functionalized piperidines has been developed based on a low-cost and environmentally benign Bi(OTf)₃ catalyst via a one-pot condensation of aromatic aldehydes, β-ketoesters and aromatic amines.

Keywords: Bi(OTf)₃, Functionalized piperidines, One-pot synthesis, Multicomponent reaction.
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INTRODUCTION

Pyridine and its partially or totally unsaturated derivatives, namely, the tetrahydropyridines, dihydropyridines and piperidines, are ubiquitous structural motifs found in natural products and in compounds of interest for the pharmaceutical, agrochemical, and other chemical industries.

Functionalized tetrahydropyridines and piperidines are common substructures found in biologically active natural products and synthetic pharmaceuticals [1].

Figure 1
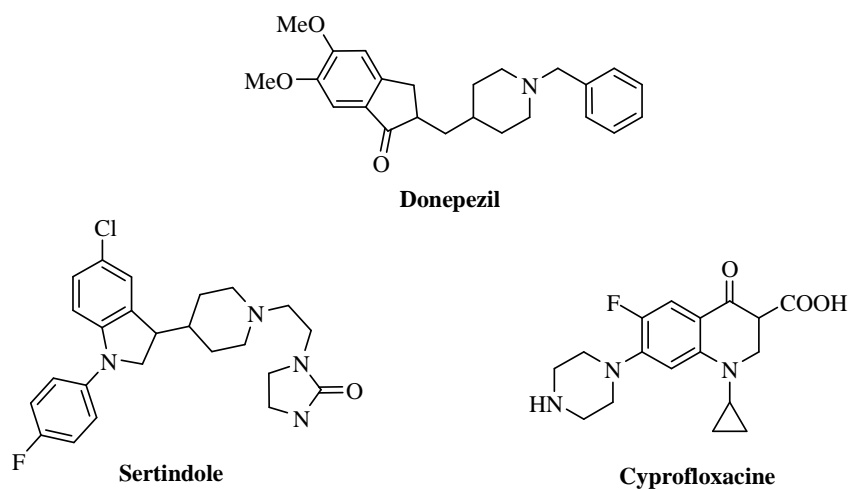
There are thousands of literature references, including patents, which utilize such compounds in medicinal research [2]. Of these, 1,4-disubstituted piperidine scaffolds are of particular importance, some as established drugs [3a], such as Donepezil [3b] which is used for treatment of Alzheimer's disease, Sirtindole [3c] and Cyprofloxacine

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[3d,e] for the treatment of Schizophrenia (Fig. 1). Some bearing piperidine frameworks (also convertible to the corresponding piperidines) are important in antiparasitic, antiviral, anticancer, antimicrobial, and antimalarial research as well as other fields [4].

For the important reasons mentioned above and due to the bioactivity of many piperidine-containing compounds [5], and although the availability of many traditional procedures for the synthesis of these heterocyclic compounds, the development of efficient and versatile methods for the enantioselective synthesis of these six-membered nitrogen heterocycles continues to be a relevant synthetic goal with the pyridines [6], and piperidines [7], having received much attention in this regard, and to be an important objective in organic chemistry [8].

Nowadays, one-pot multicomponent reactions have received special attention over their multistep variants for reasons of atome economy, energy efficiency, and general environmental friendliness [9]. Although, three reports have been made on the one-pot multicomponent synthesis of functionalized piperidines (FP) in high diastereoselectivity, based on $InCl_3$ [10a], $Me_2S^+BrBr^-$ [10b], and TFA-proline [4], $ZrOCl_2.8H_2O$ [11], $Bi(NO_3)_3.5H_2O$ [12], I_2 [13], VCl_3 [14], PEG-embedded KBr_3 [15], picric acid [16], Oxalic acid dehydrate [17], TBATB [18], [PBBS] or [TBBDA] [19], Acidic ionic liquids [20], Cerium(IV) triflate [21], and BF_3-SiO_2 [22] from the reaction of aromatic aldehydes, amines, and acetoacetic ester, these methods have limitations in terms of product diversity and yields.

During the last two decades, rare earth metal triflates mediated organic reactions have gained much attention in organic synthesis due to its low toxicity, commercial availability, moisture stability, and recyclability [23].

We herein report an efficient one-pot synthesis of highly substituted and functionalized piperidine derivatives using $Bi(OTf)_3$ as new versatile and efficient catalyst (Scheme 1).

Scheme 1
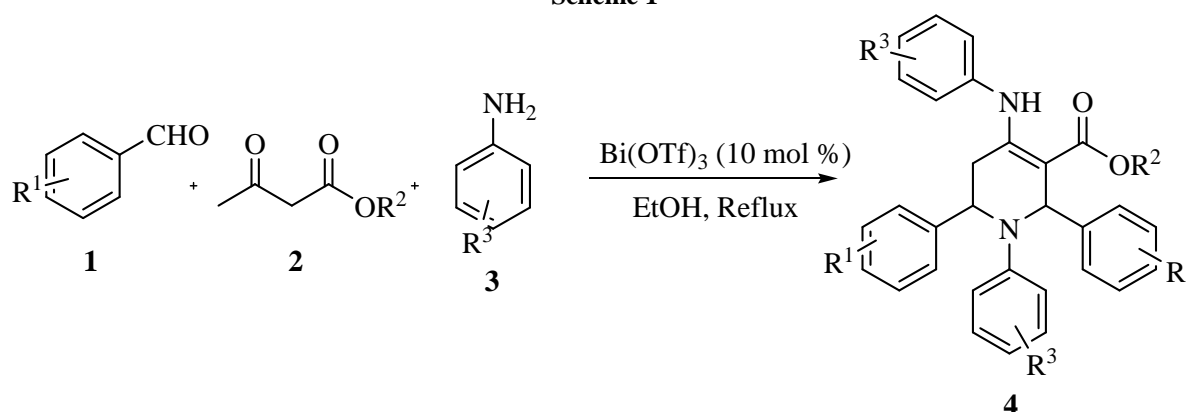
EXPERIMENTAL SECTION

General procedure for the synthesis of highly functionalized piperidines **4**.
A mixture of aniline (2 mmol), ethyl acetoacetate or methyl acetoacetate (1 mmol), and $Bi(OTf)_3$ (10 mol %) in 4 ml of ethanol were stirred at 80 °C for 20 min, then aromatic aldehyde (2 mmol) was added and stirring was continued up to completion of the reaction as indicated by TLC. After completion of the reaction, a thick precipitate was obtained. The solid was filtered and washed with cold ethanol-water, and the crude product was purified by crystallization from ethyl acetate-ethanol mixture to yield the highly pure piperidine derivatives. The physical data (M.p., IR, and NMR) of known compounds were found to be identical with those reported in the literature.

Spectroscopic data for:
Ethyl 1,2,6-triphenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4a) White crystals, mp 171-173 °C. IR (KBr) ν (cm^{-1}): 3244 (N-H), 1651 (C=O), 1589 (C=C). ^{1}H NMR (250 MHz, CDCl$_3$) δ ppm (*J*, Hz): 1.53 (3H, t, *J*=7.0 Hz, CH$_3$CH$_2$), 2,88 (1H, dd, *J*=15.0, 2.2 Hz, H-5), 2.94 (1H, dd, *J*=15.0, 2.2 Hz, H-5'), 4.32- 4.5 (2H, m, CH$_3$CH$_2$), 5.2 (1H, s, H-6), 6.33 (1H, s, H-2), 6.54-7.40 (20H, m, Ar-H), 10.37 (1H, s, NH). ^{13}C NMR (62.5 MHz, CDCl$_3$) δ ppm: 15.2; 34.0 (C-5); 55.4 (C-2); 58.6 (C-6); 60.1; 98.5 (C-3); 113.3; 116.5; 126.1; 126.2; 126,7; 127.0; 127.6; 128.7; 129.1; 129.3; 129.4; 138.2; 143.1; 144.4; 147.3; 156.5 (C-4); 168.7 (C=O).

Ethyl 2,6-bis(4-chlorophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4b) White crystals, mp 236-238 °C. IR (KBr) ν (cm^{-1}): 3421 (N-H), 1647 (C=O), 1512 (C=C), 752 (C-Cl). ^{1}H NMR (250 MHz,

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CDCl₃) δ ppm (*J*, Hz): 1.49 (3H, t, *J*=7.1 Hz, CH₃CH₂), 2,78 (1H, dd, *J*=12.4, 2.8 Hz, H-5), 2.88 (1H, dd, *J*=9.9, 5.3 Hz, H-5'), 4.32- 4.53 (2H, m, CH₃CH₂), 5.06 (1H, s, H-6), 6.41 (1H, s, H-2), 6.44 (2H, dd, *J*=6.1, 1.3 Hz, Ar-H), 6.50 (1H, d, *J*= 8.2 Hz, Ar-H), 6.51 (1H, t, *J*= 7.2 Hz, Ar-H), 7.08-7.29 (10H, m, Ar-H), 10.34 (s, 1H, NH). ¹³C NMR (62.5 MHz, CDCl₃) δ ppm: 14.7; 33.6 (C-5); 54.6 (C-2); 57.3 (C-6); 59.8; 97.6; 112.8; 116.6; 125.6; 125.9; 127.7; 128.0; 128.3; 128.7; 129.0; 129.1; 132.0; 132.7; 137.5; 140.8; 142.3; 146.4; 155.7 (C-4); 167.9 (C=O).

Ethyl 2,6-bis(4-bromophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4c) White crystals, mp 238-240 °C. IR (KBr) ν cm⁻¹: 3232 (N-H), 1651 (C=O), 1597 (C=C). ¹H NMR (250 MHz, CDCl₃) δ ppm (*J*, Hz): 1.49 (3H, t, *J*=7.1 Hz, CH₃CH₂), 2.77 (1H, dd, *J*=15.2, 2.7 Hz, H-5), 2.86 (1H, dd, *J*=15.2, 5.3 Hz, H-5'), 4.34- 4.49 (2H, m, CH₃CH₂), 5.11 (1H, s, H-6); 6.38 (1H, s, H-2), 6.44 (2H, dd, *J*=7.7, 2.0 Hz; Ar-H), 6.49 (2H, d, *J*=8.18 Hz, Ar-H), 6.68 (1H, t, *J*=7.2 Hz, CH₃CH₂), 7.02-7.25 (9H, m, Ar-H), 7.41 (2H, d, *J*=2,5 Hz, Ar-H), 7.44 (1H, d, *J*=2.6 Hz, Ar-H), 10.32 (1H s, NH). ¹³C NMR (62.5 MHz, CDCl₃) δ ppm: 15.3; 34.1 (C-5); 55.2 (C-2); 57.9 (C-6); 60.3; 98.1; 113.4; 117.2; 120.2; 120.7; 121.4; 126.1; 126.4; 128.6; 128.9; 129.5; 131.8; 132.2; 138.0; 141.9; 143.4; 146.9; 156.3 (C-4); 168.4 (C=O).

Ethyl 2,6-bis(4-nitrophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4d) Yellow crystals, mp 246-248 °C. IR (KBr) ν (cm⁻¹): 3244 (N-H), 1597 (C=O), 1255 (C=C). ¹H NMR (250 MHz, CDCl₃) δ ppm (*J*, Hz): 1.52 (3H, t, *J*=7.1 Hz, CH₃CH₂), 2.91 (2H, m, H-5, H-5'), 4.36-4.56 (2H, m, CH₃CH₂), 5.30 (1H, s large, H-6), 6.41-6.45 (5H, m, Ar-H), 6.73 (1H, t, *J*=7.3 Hz, Ar-H), 7.06 (1H, s, Ar-H), 7.10-7.19 (3H, m, Ar-H), 7.55 (4H, m, Ar-H), 8.18 (4H, t, *J*=8.2 Hz, Ar-H), 10.36 (1H, s, NH). ¹³C NMR (62.5 MHz, CDCl₃) δ ppm: 15.0; 38.0 (C-5); 55.3 (C-2); 57.5 (C-6); 60.4; 97. 0; 113.0; 117.8; 123.9; 124.1; 125.6; 126.5; 127.4; 127.5; 129.3; 129.5; 137.3; 145.9; 146.9; 147.4; 149.9; 151.8; 155.4 (C-4); 167.7 (C=O).

Ethyl 1-phenyl-4-(phenylamino)-2,6-di-*p*-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylate (4e) White crystals, mp 234-235°C. IR (KBr) ν (cm⁻¹): 3232 (N-H), 1651(C=O), 1597 (C=O). ¹H NMR (250 MHz, CDCl₃) δ ppm (*J*, Hz): 1.52 (3H, t, *J*=7.1 Hz, CH₃CH₂), 2.39 (6H, s, 2CH₃), 2,82 (1H, dd, *J*=12.6, 2.5 Hz, H-5), 2.93 (1H, dd, *J*=9.6, 5.4 Hz, H-5'), 4.34- 4.55 (2H, m, CH₃CH₂), 5.18 (1H, s large, H-6), 6.35 (2H, d, *J*=8.2 Hz, Ar-H), 6.48 (1H, s, Ar-H), 6.59 (2H, d, *J*=8.4 Hz, Ar-H), 6.65 (1H, t, *J*=7.2 Hz, Ar-H), 7.09-7.30 (11H, m, Ar-H), 7.27 (2H, d, *J*= 8.0 Hz, Ar-H), 10.36 (1H, s, NH). ¹³C NMR (62.5 MHz, CDCl₃) δ ppm: 15.2; 21.5; 21.6; 34.1 (C-5); 55.2 (C-2); 58.4 (C-6); 60.1; 98.7; 113.3; 116.4; 126.0; 126.2; 126.7; 126,9; 129.2; 129.3; 129.4; 129.7; 136.2; 137.0; 138.4; 140.1; 144.4; 147.5; 156.5 (C-4); 168.7 (C=O).

Methyl 2,6-bis(4-phenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4f) White crystals, mp 182-184 °C. IR (KBr) ν (cm⁻¹): 3242 (N-H), 2945, 1650 (C=O), 1598 (C=C). ¹H NMR (250 MHz, CDCl₃) δ ppm (*J*, Hz): 2.75 (1H, dd, *J*= 15.2, 2.7 Hz, H-5), 2.82 (1H, dd, *J*= 15.2, 5.3 Hz, H-5'), 3.94 (3H, s, COCH₃), 5.22 (1H, s, H-6), 6.35 (1H, s, H-2), 6.52-7.42 (00 H, m, Ar-H), 10.2 (1H, s, NH). ¹³C NMR (62.5 MHz, CDCl₃) δ ppm: 34.2 (C-5); 51.7; 55.2 (C-2); 57.8 (C-6); 98.0; 113.4; 117.2; 126.2; 126.5; 128.2; 128.5; 128.9; 129.3; 129.5; 129.6; 132.6; 133.4; 138.1; 141.4; 142.8; 146.9; 156.5 (C-4); 168.8 (C=O).

Methyl 2,6-bis(4-chlorophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4g) White crystals, mp 200-202 °C. IR (KBr) ν (cm⁻¹): 3240 (N-H), 2947, 1655 (C=O), 1593 (C=C), 744 (C-Cl). ¹H NMR (250 MHz, CDCl₃) δ ppm, (*J*, Hz): 2.79 (1H, dd, *J*= 15.2, 2.7 Hz, H-5), 2.88 (1H, dd, *J*= 15.2, 5.3 Hz, H-5'), 3.97 (3H, s, COCH₃), 5.15 (1H, s, H-6), 6.41 (1H, s, Ar-H), 6.44 (2H, dd, *J*= 7.6, 2.1 Hz, Ar-H), 6.55 (2H, d, *J*= 8.1 Hz, Ar-H), 7.09 (2H, d, *J*= 1.4 Hz, Ar-H), 7.12-7.30 (10 H, m, Ar-H), 10.3 (1H, s, NH). ¹³C NMR (62.5 MHz, CDCl₃) δ ppm: 34.2 (C-5); 51.7; 55.2 (C-2); 57.8 (C-6); 98.0; 113.4; 117.2; 126.2; 126.5; 128.2; 128.5; 128.9; 129.3; 129.5; 129.6; 132.6; 133.4; 138.1; 141.4; 142.8; 146.9; 156.5 (C-4); 168.8 (C=O).

Methyl 2,6-bis(4-bromophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4h) White crystals, mp 228-230 °C. IR (KBr) ν (cm⁻¹): 3240 (N-H), 1655 (C=O), 1593 (C=C), 744 (C-Cl). ¹H NMR (250 MHz, CDCl₃) δ ppm (*J*, Hz): 2.76 (1H, d, *J*=15.2 Hz, H-5), 2.86 (1H, dd, *J*=15.1, 5.1 Hz, H-5'), 3.95 (3H, s, COCH₃), 5.11 (1H, s, H-6), 6.41-6.49 (4H, m, Ar-H), 6.68 (3H, t, *J*=7.0 Hz, Ar-H), 7.02 (2H, d, *J*=8.0 Hz, Ar-H), 7.10 (2H, d, *J*=7.8 Hz, Ar-H), 7.14-7.22 (5H, m, Ar-H), 7.42 (4H, d, *J*=7.7 Hz, Ar-H), 10.28 (1H, s, NH). ¹³C NMR (62.5 MHz, CDCl₃) δ ppm: 34.3(C-5); 51.9; 55.4 (C-2); 58.1 (C-6); 98.0; 113.5; 117.4; 120.9; 121.6; 126.4; 126.8; 128.8; 129.1; 129.7; 132.0; 132.4; 138.2; 142.1; 143.5; 147.0; 156.7 (C-4); 169.0 (C=O).

Ethyl 2,6-bis(4-bromophenyl)-1-(4-fluorophenyl)-4-(4-fluorophenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4i) White crystals, mp 220-222 °C. IR (KBr) ν cm⁻¹: 3232 (N-H), 2982 (C=O), 1585 (C=C), 810 (C-Br). ¹H NMR (250 MHz, CDCl₃) δ ppm (*J*, Hz): 1.47 (3H, t, *J*=7.1 Hz, CH₃CH₂), 2.63 (1H, dd, *J*=15.3, 2.6 Hz, H-5), 2.80 (1H, dd, *J*=15.2, 5.5 Hz, H-5'), 5.04 (1H, s, H-6), 6.35- 6.40 (4H, m, Ar-H), 6.72-6.90 (4H, m, Ar-H), 7.03 (2H, d, *J*= 8.4 Hz, Ar-H), 7.14 (2H, d, *J*= 11.1 Hz, Ar-H), 7.37- 7.43 (4H, m, Ar-H), 10.22 (1H, s, NH). ¹³C NMR

(62.5 MHz, CDCl$_3$) δ ppm: 15.3; 31.5; 34.1 (C-5); 55.9 (C-2); 58.1 (C-6); 60.5; 98.1; 114.4; 114.5; 115.8; 116.2; 120.9; 121.7; 128.4; 128.5; 128.7; 131.9; 132.4; 134.1; 141.9; 143.1; 156.3 (C-4); 168.5 (C=O).

RESULTS AND DISCUSSION

The reaction of 2 equivalents of benzaldehyde **1a** with 1 equivalent of ethyl acetoacetate **2a** and 2 equivalents of aniline **3a** was initially carried in ethanol, without the use of catalyst. The reaction was very slow, and the yield was disappointing because it was significantly low compared to that reported in the previous papers (Entry 1, Table 1). In order to improve the yield, we chose Bismuth triflate as catalyst. The results summarized in Table 1 show that the previous condensation proceeded efficiently in the presence of 5 mol % of Bi(OTf)$_3$, but resulting in a very modest yield of the desired product (entry 2). Then, we used different catalyst's amounts to promote the condensation. We found that the product **4a** was formed in near a quantitative yield when 10 mol% of the catalyst were used (Entry 3). When we increased the amount of the catalyst to 15 or 20 mol%, the reactions afforded bad results (Entries 4 and 5). By optimizing further the reaction conditions, it was found that the reaction in 50 % aqueous ethanol or by using acetonitrile as solvents, allowed the condensation to be performed however the corresponding tetrahydropyridine was obtained in lower yield (Entries 6 and 8). However, the same reaction carried out in water don't work at all (Entry 7).

Table 1. Optimization of reaction conditions for the synthesis of highly substituted tetrahydropyridines[a]
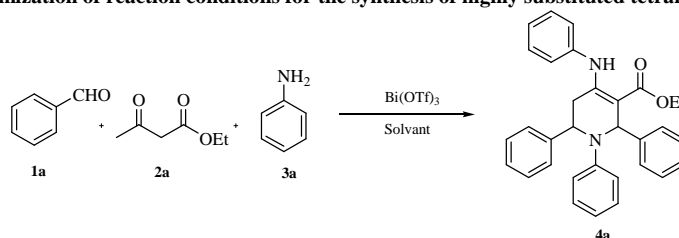
Entry	Solvent	Catalyst	Catalyst (mol %)	Time (h)	Yield[b] (%)
1	EtOH	-	-	24	trace
2	EtOH	Bi(OTf)$_3$	5	7	24
3	EtOH	Bi(OTf)$_3$	10	7	66
4	EtOH	Bi(OTf)$_3$	15	7	28
5	EtOH	Bi(OTf)$_3$	20	7	26
6	EtOH /H$_2$O (1/1)	Bi(OTf)$_3$	10	7	30
7	H$_2$O	Bi(OTf)$_3$	10	7	-
8	CH$_3$CN	Bi(OTf)$_3$	10	7	29
9	EtOH	Bi(NO$_3$)$_3$.5H$_2$O	10	2.5	29
10	EtOH	Bi$_2$O$_3$	10	24	trace
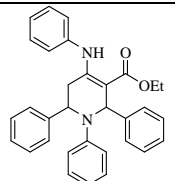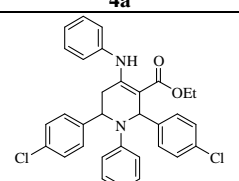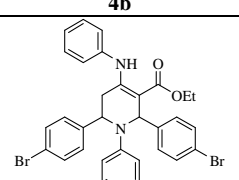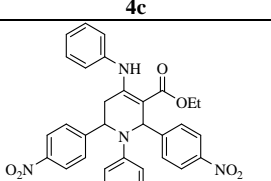
[a] *Reaction conditions: A mixture of benzaldehyde (2 mmol), aniline (2 mmol), and ethyl acetoacetate (1 mmol).*
[b] *Isolated yields.*

Given the successful development of this new procedure, we were prompted to study the generality of this Bi(OTf)$_3$-mediated tetrahydopyridi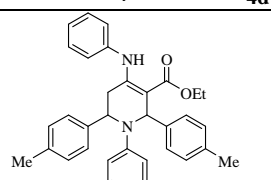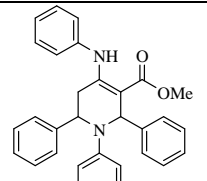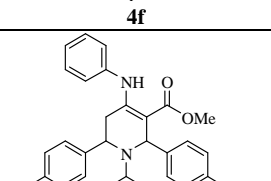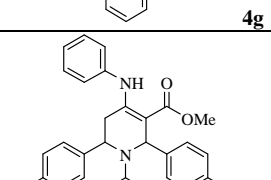ne synthesis with various substrates. Table 2 lists several of the prepared products. To explore the scope of this methodology, reactions were performed with various aromatic aldehydes with aniline and ethyl acetoacetate under the same reaction conditions (Table 2, entries 1-5). A variety of electron-rich or electron poor aldehydes with various substitution patterns smoothly underwent the transformation to give the corresponding products in good yields. However, 3-iodobenzaldehyde and 2-nitroaniline did not give the desired products because of the steric hindrance caused by the large iodo and nitro groups respectively. Also, 4-methoxybenzaldehyde remained unaffected under the reaction conditions probably due to the strong electron donating effect of the OMe group, which reduces the electrophilicity of the aldehyde group.

The present protocol was also examined for other 1,3-dicarbonyl compound such as methyl acetocetate, with varying aromatic aldehydes and aniline, where the desired piperidine derivatives **4a-i** were obtained in good yields as shown in Table 2 (entries 6 and 7). This establishes that the alkoxy moiety present in the ester functionality does not have any major role in determining the course of the reaction.

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Table 2. Bi(OTf)$_3$-Catalyzed synthesis of tetrahydropyridines under optimized reaction conditions[a]

Entry	R^1	R^2	R^3	product	Time (h)	Yield[b] (%)	M.p. (° C) Measured	Reported
1	H	Et	H	**4a**	7	66	171-173	178 [20]
2	4-Cl	Et	H	**4b**	4	82	236-238	234-236 [20]
3	4-Br	Et	H	**4c**	10	73	238-240	234-236 [16]
4	4-NO$_2$	Et	H	**4d**	4	75	246-248	247-249 [24]
5	4-Me	Et	H	**4e**	2	61	234-235	232 [20]
6	H	Me	H	**4f**	8	70	182-184	180-182 [20]
7	4-Cl	Me	H	**4g**	6	64	200-202	193 [25]
8	4-Br	Me	H	**4h**	6	81	228-230	228-230 [24]

9	4-Br	Et	4-F	**4i**	10	63	220-222	218 [22]

ᵃ Reaction conditions: A mixture of aromatic aldehydes (2 mmol), anilines (2 mmol), and ethyl/methyl acetoacetate (1 mmol) in the presence of bismuth triflate (10 mol%) as catalyst.
*ᵇ Isolated yields.*

To find the generality and scope of this MCR, other amines were also examined. Anilines bearing electron-withdrawing groups such as NO_2 did not give any product, nevertheless, *p*-fluroaniline led to the desired piperidine in moderate yield (entry 8) although a prolonged reaction time (10 hours) was required. The low reactivity of anilines containing electron-withdrawing groups can be attributed to their relatively weak nucleophilicity and therefore decreased activity in the Mannich steps of the reaction.

Most of the reactions afforded the corresponding THPs in good to excellent yields irrespective of the position of the substituents present in aldehyde or amine. Work-up was simple and for all the substrates, the following procedure was adopted. Once the reaction was deemed complete (no further conversion in TLC), the precipitated product was collected by filtration. In all cases, simple washing with cold ethanol and crystallization from ethyl acetate/ethanol delivered the desired product in very pure form.

Finally, we proposed in scheme **2**, a plausible mechanism in which benzaldehyde **1** was reacted with enamine **5**, which was formed initially from condensation of aniline with β-ketoester and the resulting probable Knovenagel product **6** or **7** was then refluxed with pure imine **8** (obtained from the reaction of aniline and aldehyde), and eventually generating **4**.
A second possible mechanism is initiated by the nucleophilic attack by enamine **5** will take place preferentially on the imine **6** to give Mannich type product **9**. Then the intermediate **9** reacts with aldehyde to give **10** after dehydration. Further, there will be a spontaneous tendency in the presence of the catalyst for tautomerization to give the intramolecular hydrogen bonded species **11**. However, the tautomer **11** immediately undergoes intramolecular Mannich-type reaction to form intermediate **12** which give by tautomerization the final piperidine derivative **4**.

Scheme 2
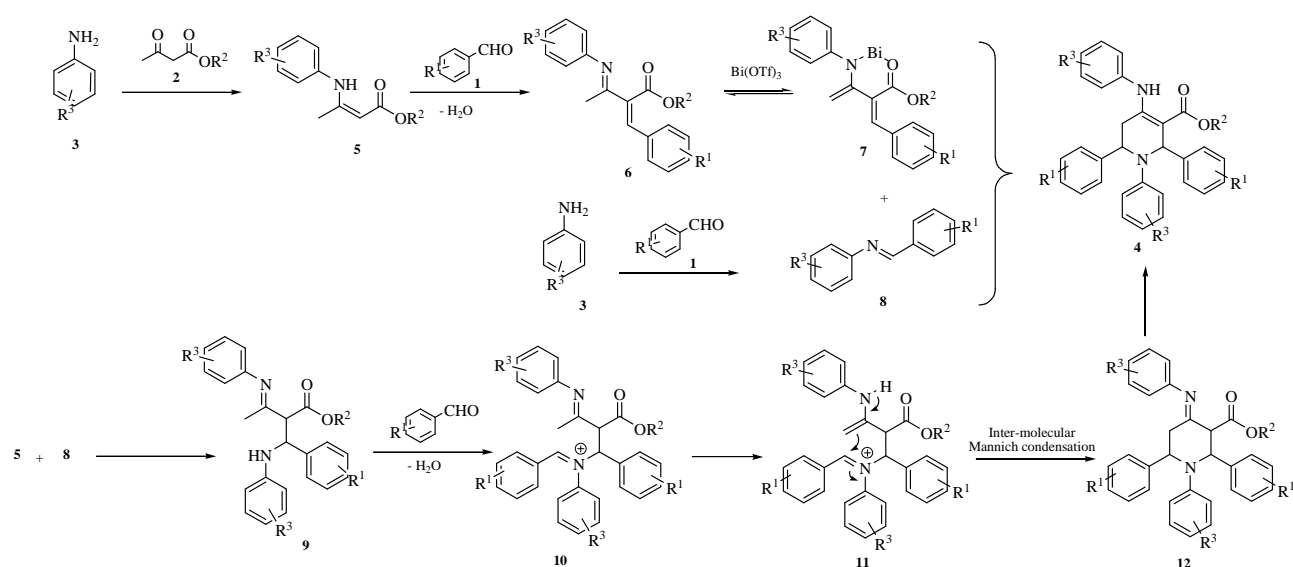
In summary, we have developed a mild and efficient reaction between aldehydes, anilines and β-ketoesters leading to piperidines using catalytic $Bi(OTf)_3$ with high atom economy. The notable advantages of this method are operational simplicity, use of inexpensive catalyst, mild reaction conditions, ease of isolation of products and non-toxic ethanol as solvent. Due to easy availability of the starting materials, the reaction might prove to be very useful for building up piperidine scaffolds.

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