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Multicomponent reaction for the synthesis of highly functionalized piperidine scaffolds catalyzed by TMSI

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Abstract

An efficient method for the synthesis of highly functionalized piperidines via one-pot domino reaction of β-ketoesters, aromatic aldehydes, and aromatic amines was reported. This multicomponent coupling was catalyzed by TMSI in methanol at room temperature, giving desired substituted pyridines in moderate to good yields.

Keywords TMSI · Highly functionalized piperidines · Multicomponent reactions · Heterocycles

Introduction

The piperidine ring system is one of the most regular motifs found in many naturally occurring alkaloids [1–5], synthetic pharmaceuticals, and biologically active compounds [6]. For example, 1,4-disubstituted piperidine scaffolds have been used as established drugs [7–9] because of their wide range of biological activities such as anti-bacterial [10], antimalarial [11], anti-inflammatory [12], anticonvulsant [13], and antihypertensive activities [14]. Furthermore, substituted piperidines have been identified as an important class of therapeutic agents in the treatment of cancer metastasis [15, 16], schizophrenia [17, 18], Parkinson's disease [19, 20], influenza

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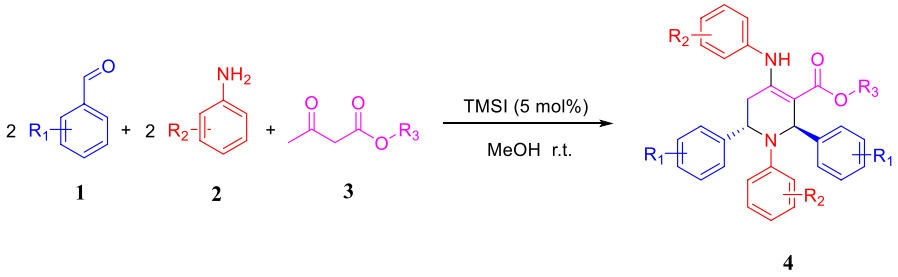
infection [21–23], viral infections including AIDS [24, 25], obesity, and diabetes [26, 27].

In the perspective of green chemistry, the main challenge for organic chemists is to develop synthetic routes to selectively prepare molecular scaffolds with structural diversity under eco-benign conditions. On this account, multicomponent reactions (MCRs) have already emerged as a useful tool for the construction of complex and novel molecular structures due to their advantages over conventional multistep synthesis [28–33]. These reactions constitute an especially remarkable synthetic protocol since they provide rapid and easy access to large libraries of organic compounds with diverse substitution patterns. Furthermore, MCRs are more environmentally benign and atom economic as they avoid time-consuming and protection–deprotection steps, as well as costly purification processes [34]. In recent years, the synthesis of highly functionalized piperidines has been reported via five-component reaction involving one molecule of β-ketoester, two molecules of aldehyde, and two molecules of substituted aniline in the presence of various catalysts. Ionic liquids are good catalyst to synthesis of these compounds, and many different kinds of ionic liquid-mediated reactions for synthesizing highly functionalized piperidines have already been described [35–39]. Organic acids including picric acid [40], tartaric acid [41], citric acid [42], PSSA [43], oxalic acid dehydrate [44], and (±)-CSA [45]; Lewis acids such as $Bi(NO_3)_3.5H_2O$ [46], $ZrOCl_2.8H_2O$ [47], SbI_3 [48], $InCl_3$ [6], $Ce(OTf)_4$ [49], $LaCl_3.7H_2O$ [50], $TiCl_2.2H_2O$ [51], $NiCl_2.6H_2O$ [52], and $Fe(NO_3)_3.9H_2O$ [53] are efficient catalysts for the synthesis of highly functionalized piperidines according to literatures. In addition, nanopowder [54–62] and graphene oxide [63] also can be used to promote the formation of highly functionalized piperidines. Although the reported catalysts have been used in the synthesis of functionalized piperidines widely, they still suffer from disadvantages such as the need of commercially unavailable reactants or catalysts, overuse of reagent, toxic solvents, relatively harsh conditions, and tedious work-up procedures. Hence, the development of a facile, high-yielding, and environmental benign protocol for the one-pot multicomponent synthesis of densely functionalized piperidine scaffolds is still necessary.

As the catalytic effect of TMSI in organic synthesis is well established [64], we applied TMSI to promote the formation of highly functionalized piperidines in this work. In continuation of our interests in organic synthesis [65–70], herein, we describe the construction of densely functionalized piperidines via one-pot multicomponent reactions of β-ketoester, aldehyde and aniline catalyzed by TMSI (Scheme 1). The desired compounds were crystallized directly from methanol and isolated through simple filtration followed with methanol washing.

Results and discussion

Readily available commercial reagents aniline, methyl acetoacetate, and 2-fluorobenzaldehyde were used for model reaction. Methylacetoacetate **3a** (MAA, 1 mmol) and aniline **2a** (2 mmol) were stirred at room temperature for 30 min to form the enamine intermediate followed by the addition of 2-fluorobenzaldehyde **1d** (2 mmol).



Scheme 1 Synthesis of highly functionalized piperidines catalyzed by TMSI

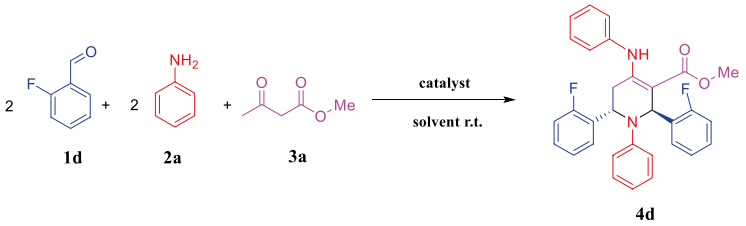
Then, the reaction mixture was further stirred till the complete formation of product **4d**.

Firstly, we focused on the screening of catalysts. No desired product was obtained in the blank experiment in methanol (Table 1, entry 1). When 0.2 equiv. of trimethylsiylchloride (TMSCl) was added, piperidine **4d** was isolated in the yield of 85% (Table 1, entry 2). Next, other catalysts such as *tert*-butyldimethylsiyl chloride (TBSCl), acetyl chloride, chloroacetyl chloride, benzoyl chloride, and acetyl bromide were tested, and they all gave good results (Table 1, entries 3–7). A better result was obtained when using 0.2 equiv. of TMSI, which produced compound **4d** in the yield of 91%. We found that the yield was not affected by gradually reducing the amount of catalyst (from 0.2 to 0.1 and then to 0.05 equiv.) (Table 1, entries 8–10). But too less loading of TMSI (0.02 equiv.) caused a sharp drop of yield (Table 1, entry 11). We also examined other solvents including ethanol, *iso*-propanol, *tert*-butanol, ethylene glycol, glycerol, acetonitrile, and tetrahydrofuran under same conditions (Table 1, entries 12–18). The experiment results showed that methanol was the best choice for the reaction.

With the optimal reaction conditions in hand, we then examined the generality and scope of this five-component reaction using a variety of aromaticaldehydes, aromaticamines, and β-ketoesters, and the outputs are summarized in Table 2. The mixture of 4-methoxybenzaldehyde and aniline reacted with MAA under the standard conditions, giving highly functionalized piperidine **4a** in the yield of 74% (Table 2, entry 1). In general, aromatic aldehydes bearing electron-donating or electron-withdrawing functional groups at different positions can react with methyl acetoacetate smoothly in the presence of aniline and the yields of corresponding products in good to excellent yields (Table 2, entries 2–4). Besides substituted benzaldehyde, aromatic heterocyclic aldehyde was also suitable for this reaction and the yield of corresponding product was satisfactory (Table 2, entry 5). In contrast, aliphatic aldehydes such as *n*-hexanal and isobutyraldehyde did not give their corresponding functionalized piperidines (not shown in the table).

4-Chloroaniline and *p*-anisidine were also tolerated, which gave corresponding tetrahydropyridine derivatives in moderate to good yields (Table 2, entries 6–12). Finally, other β-ketoester such as ethyl acetoacetate was tested. The alkoxy moiety presents small or no influence on the reaction, and the yields obtained were generally good (Table 2, entries 13–18). All the known synthesized compounds and their relative

Table 1 Screening of optimal reaction conditions

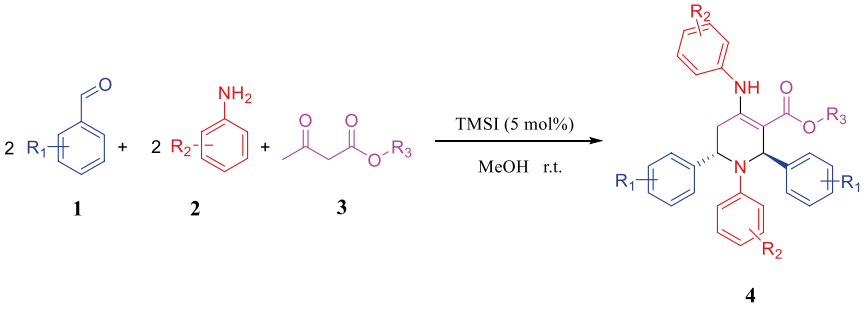


Entry	Catalyst (equiv.)	Solvent	Temperature (°C)	Time (h)	Isolated yield (%)
1	–	methanol	r.t	24	–
2	TMSCl (0.20)	methanol	r.t	24	85
3	TBSCl (0.20)	methanol	r.t	24	86
4	AcCl (0.20)	methanol	r.t	24	78
5	ClAcCl (0.20)	methanol	r.t	24	81
6	BzCl (0.20)	methanol	r.t	24	88
7	AcBr (0.20)	methanol	r.t	24	89
8	TMSI (0.20)	methanol	r.t	24	91
9	TMSI (0.10)	methanol	r.t	24	93
10	**TMSI (0.05)**	**methanol**	**r.t**	**24**	**94**
11	TMSI (0.02)	methanol	r.t	24	76
12	TMSI (0.05)	thanol	r.t	24	91
13	TMSI (0.05)	*iso*-propanol	r.t	24	89
14	TMSI (0.05)	*tert*-butanol	r.t	24	43
15	TMSI (0.05)	Ethylene glycol	r.t	24	24
16	TMSI (0.05)	glycerol	r.t	24	trace
17	TMSI (0.05)	acetonitrile	r.t	24	62
18	TMSI (0.05)	tetrahydrofuran	r.t	24	49

stereochemistry were confirmed by carefully comparing their spectral data and physical properties with the reported literature.

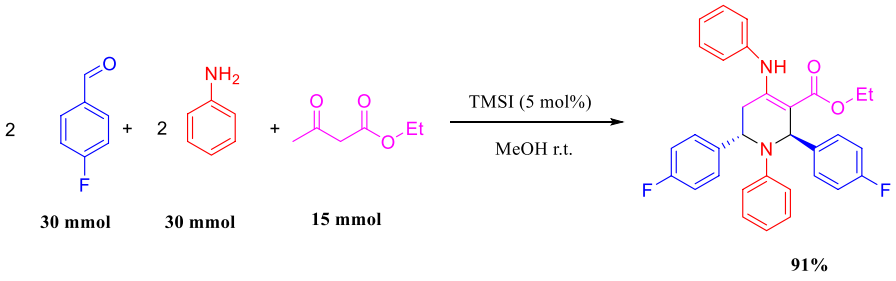
The same excellent results were also obtained when this method was performed at a gram scale using 4-fluorobenzaldehyde, aniline and EAA as substrates (Scheme 2). This example clearly demonstrates the preparative utility of this newly developed method.

Table 2 Synthesis of **4** under optimum conditions[a]



Entry	R_1	R_2	R_3	Product	Yield (%)[b]
1	4-$MeOC_6H_4$	C_6H_5	Me	**4a**	74
2	C_6H_5	C_6H_5	Me	**4b**	87
3	4-MeC_6H_4	C_6H_5	Me	**4c**	84
4	2-FC_6H_4	C_6H_5	Me	**4d**	94
5	2-Thenyl	C_6H_5	Me	**4e**	80
6	4-$MeOC_6H_4$	4-ClC_6H_4	Me	**4f**	80
7	C_6H_5	4-ClC_6H_4	Me	**4g**	87
8	4-FC_6H_4	4-ClC_6H_4	Me	**4h**	94
9	2-Thenyl	4-ClC_6H_4	Me	**4i**	82
10	C_6H_5	4-$MeOC_6H_4$	Me	**4j**	72
11	2-FC_6H_4	4-$MeOC_6H_4$	Me	**4k**	81
12	2-Thenyl	4-$MeOC_6H_4$	Me	**4l**	48
13	4-$MeOC_6H_4$	C_6H_5	Et	**4m**	75
14	4-MeC_6H_4	C_6H_5	Et	**4n**	89
15	C_6H_5	C_6H_5	Et	**4o**	73
16	4-FC_6H_4	C_6H_5	Et	**4p**	95
17	4-ClC_6H_4	C_6H_5	Et	**4q**	85
18	4-FC_6H_4	4-$MeOC_6H_4$	Et	**4r**	76

[a]reaction conditions: **1** (4 mmol), **2** (4 mmol), **3** (2 mmol), methanol (10 mL), TMSI (0.1 mmol) at room temperature. [b]isolated yield.



Scheme 2 Synthesis of **4t** on gram scale

Experimental

General information

All reagents were purchased from Adamas (China) and were used without further purification. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) with silica gel plates (60F-254) using UV light. Yields refer to pure compounds. Melting points were measured on an electrothermal 9100 apparatus. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 400 MHz or 600 MHz spectrometer as indicated in the data list. Chemical shifts for proton nuclear magnetic resonance (^{1}H NMR) spectra are reported in parts per million relative to the signal residual ($CDCl_3$ at7.26 ppm) or TMS. Chemical shifts for carbon nuclear magnetic resonance (^{13}C NMR) spectra are reported in parts per million relative to the center line of the $CDCl_3$ triplet at 77.06 ppm. The abbreviations s, d, dd, t, q, br, and m stand for the resonance multiplicity singlet, doublet, doublet of doublets, triplet, quartet, broad, and multiplet, respectively.

General procedure for the synthesis ofpiperidines (4a-4r)

A mixture of *β*-ketoester (2 mmol) and aromatic aniline (4 mmol) in methanol (10 ml) in the presence of TMSI (0.1 mmol) was stirred for 30 min at room temperature, followed by the addition of aromatic aldehyde (4 mmol). The resulting mixture was continuously stirred until the completion of reaction. Then, the reaction mixture was concentrated and the precipitate was filtered off. Finally, the solids were washed with methanol (5 mL) to give pure products.

Methyl 2,6-bis(4-methoxyphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**4a**) white solid. Mp: 188–189 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.27 (s, 1H, NH), 7.21 (d, J=8.5 Hz, 2H), 7.14 – 7.02 (m, 7H), 6.81 (d, J=8.5 Hz, 4H), 6.60 (t, J=7.2 Hz, 1H), 6.52 (d, J=8.2 Hz, 2H), 6.35 (m, 3H), 5.08 (d, J=3.3 Hz, 1H), 3.92 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 2.85 (dd, J=15.0, 5.5 Hz, 1H), 2.75 (dd, J=15.0, 2.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.97, 158.08, 157.45, 155.73, 146.39, 137.32, 135.25, 134.02, 128.24, 127.07, 126.82, 125.15, 125.04, 115.44, 113.37, 112.95, 112.35, 97.51, 56.87, 54.67, 54.60, 53.95, 50.35, 33.11.

Methyl 1,2,6-triphenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**4b**) white solid. Mp: 170–172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.25 (s, 1H), 7.34–7.24 (m, 8H), 7.20–7.15 (m, 2H), 7.11–7.04 (m, 5H), 6.60 (t, J=7.2 Hz, 1H), 6.52 (d, J=8.2 Hz, 2H), 6.45 (s, 1H), 6.31–6.23 (m, 2H), 5.15 (d, J=4.2 Hz, 1H), 3.93 (s, 3H), 2.87 (dd, J=15.1, 5.7 Hz, 1H), 2.76 (dd, J=15.1, 2.3 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.94, 155.64, 146.32, 143.30, 142.10, 137.20, 128.25, 128.21, 128.00, 127.61, 126.51, 126.01, 125.76, 125.68, 125.24, 125.14, 115.54, 112.30, 97.32, 57.57, 54.49, 50.38, 32.99.

Methyl 2,6-bis(4-methphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**4c**) white solid. Mp: 210–212 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.25 (s, 1H), 7.19 (d, J=7.9 Hz, 2H), 7.12–7.02 (m, 11H), 6.59 (t, J=7.3 Hz, 1H), 6.52 (d,

J = 8.3 Hz, 2H), 6.39 (s, 1H), 6.33–6.25 (m, 2H), 5.11 (d, *J* = 3.9 Hz, 1H), 3.92 (s, 3H), 2.86 (dd, *J* = 15.0, 5.6 Hz, 1H), 2.75 (dd, *J* = 15.1, 2.2 Hz, 1H), 2.33 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.97, 155.64, 146.44, 140.33, 139.06, 137.33, 135.97, 135.14, 128.63, 128.30, 128.21, 128.17, 126.12, 125.92, 125.69, 125.18, 124.99, 115.37, 112.28, 97.49, 57.29, 54.30, 50.34, 33.02, 20.46, 20.38.

Methyl 2,6-bis(2-fluorophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**4d**) white solid. Mp: 178–180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.15 (s, 1H), 7.266.95 (m, 13H), 6.65 (t, *J* = 7.3 Hz, 1H), 6.55 (s, 1H), 6.48 (d, *J* = 8.2 Hz, 2H), 6.38–6.36 (m, 2H), 5.45 (s, 2H), 3.89 (s, 3H), 2.932.87 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.85, 160.86, 160.19, 159.22, 158.57, 154.93, 145.69, 137.27, 129.16, 129.07, 128.41, 128.32, 128.26, 128.21, 127.72, 127.67, 125.25, 125.15, 123.75, 122.76, 116.30, 115.86, 115.71, 114.60, 114.45, 112.34, 96.07, 51.65, 51.47, 50.42, 30.41.

Methyl 2,6-bis(2-thenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**4e**) white solid. Mp: 220–222 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.61 (s, 1H), 7.31 (t, *J* = 7.8 Hz, 2H), 7.27–7.11 (m, 5H), 7.08–7.02 (m, 2H), 6.98 (t, *J* = 8.8 Hz, 5H), 6.85–6.75 (m, 2H), 6.16 (s, 1H), 4.90 (dd, *J* = 11.3, 4.4 Hz, 1H), 3.75 (s, 3H), 3.04–2.75 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.54, 156.66, 152.06, 149.30, 147.73, 137.68, 128.72, 128.42, 128.23, 128.10, 126.47, 125.85, 125.02, 124.51, 123.94, 123.47, 123.42, 123.38, 12,331, 118.64, 115.75, 112.75, 97.85, 58.90, 55.36, 50.42, 36.33.

Methyl 2,6-bis(4-methoxyphenyl)-1-(4-chlorophenyl)-4-((4-chlorophenyl) amino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**4f**) white solid. Mp:199–200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.22 (s, 1H), 7.16 (d, *J* = 8.6 Hz, 2H), 7.06 (m, 4H), 6.99 (d, *J* = 9.0 Hz, 2H), 6.86–6.78 (m, 4H), 6.42 (d, *J* = 9.1 Hz, 2H), 6.28 (s, 1H), 6.25 (d, *J* = 8.5 Hz, 2H), 5.04 (d, *J* = 3.8 Hz, 1H), 3.93 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 2.83 (dd, *J* = 15.1, 5.6 Hz, 1H), 2.68 (dd, *J* = 15.0, 2.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.86, 158.31, 157.63, 155.03, 144.91, 135.84, 134.44, 133.43, 130.72, 128.41, 128.04, 126.94, 126.75, 126.35, 120.52, 113.52, 113.45, 113.07, 98.02, 56.98, 54.70, 54.61, 54.13, 50.51, 32.97.

Methyl 2,6-bisphenyl-1-(4-chlorophenyl)-4-((4-chlorophenyl)amino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**4g**) white solid. Mp: 200–202 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 1H), 7.32–7.21 (m, 8H), 7.17–7.12 (m, 2H), 7.05 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 9.0 Hz, 2H), 6.43 (t, *J* = 6.2 Hz, 2H), 6.38 (s, 1H), 6.16 (d, *J* = 8.5 Hz, 2H), 5.11 (d, *J* = 4.6 Hz, 1H), 3.94 (s, 3H), 2.85 (dd, *J* = 15.1, 5.8 Hz, 1H), 2.69 (dd, *J* = 15.1, 2.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.84, 154.96, 144.85, 142.54, 141.62, 135.74, 130.85, 128.62, 128.41, 128.10, 127.76, 126.85, 126.47, 125.97, 125.88, 125.67, 120.64, 113.40, 97.85, 57.68, 54.67, 50.56, 32.85.

Methyl 2,6-bis(4-fluorophenyl)-1-(4-chlorophenyl)-4-((4-chlorophenyl)amino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**4h**) white solid. Mp: 175–177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.22 (s, 1H), 7.21 (dd, *J* = 8.3, 5.4 Hz, 2H), 7.15–7.04 (m, 4H), 6.98 (m, 6H), 6.38 (d, *J* = 9.1 Hz, 2H), 6.32–6.26 (m, 3H), 5.07 (d, *J* = 3.7 Hz, 1H), 3.93 (s, 3H), 2.82 (dd, *J* = 15.2, 5.6 Hz, 1H), 2.68 (dd, *J* = 15.1, 2.1 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.65, 162.28, 161.83, 160.65, 160.21, 154.77, 144.49, 138.02, 136.92, 135.58, 131.06, 128.55, 128.21,

127.43, 127.24, 127.19, 126.27, 121.12, 115.13, 114.99, 114.68, 114.64, 114.45, 113.48, 97.66, 56.77, 54.18, 50.66, 33.03.

Methyl 2,6-bis(2-thenyl)-1-(4-chlorophenyl)-4-((4-chlorophenyl)amino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**4i**) white solid. Mp: 215–216 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.37 (s, 1H), 7.19–7.10 (m, 4H), 7.05 (t, J = 6.5 Hz, 2H), 6.89 (m, 2H), 6.81 (s, 2H), 6.65 (d, J = 9.1 Hz, 2H), 6.47 (d, J = 8.5 Hz, 2H), 6.35 (s, 1H), 5.36 (s, 1H), 3.90 (s, 3H), 3.09 (dd, J = 15.3, 5.3 Hz, 1H), 2.83 (dd, J = 15.3, 2.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.28, 154.90, 147.71, 146.02, 144.02, 135.86, 130.86, 128.61, 128.11, 126.25, 125.15, 125.95, 123.91, 123.79, 123.51, 123.15, 121.69, 113.88, 97.22, 53.11, 52.02, 50.51, 33.53.

Methyl 2,6-bisphenyl-1-(4-methoxyphenyl)-4-((4-methoxyphenyl)amino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**4j**) white solid. Mp: 223–225 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.10 (s, 1H), 7.40–7.08 (m, 10H), 6.63 (m, 4H), 6.43 (d, J = 9.0 Hz, 2H), 6.34 (s, 1H), 6.18 (d, J = 8.6 Hz, 2H), 5.05 (d, J = 3.2 Hz, 1H), 3.91 (s, 3H), 3.74 (s, 3H), 3.65 (s, 3H), 2.79 (dd, J = 14.9, 5.4 Hz, 1H), 2.63 (d, J = 15.1 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.01, 157.20, 156.39, 150.29, 143.65, 142.62, 140.94, 130.04, 127.97, 127.51, 127.26, 126.44, 126.16, 125.89, 125.59, 113.89, 113.41, 113.33, 96.39, 57.62, 55.07, 55.02, 54.75, 50.25, 32.94.

Methyl 2,6-bis(2-fluorophenyl)-1-(4-methoxyphenyl)-4-((4-methoxyphenyl)amino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**4k**) white solid. Mp: 202–204 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (s, 1H), 7.18 (m, 4H), 7.09–6.91 (m, 4H), 6.66 (m, 4H), 6.52–6.27 (m, 5H), 5.32 (t, J = 4.3 Hz, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.66 (s, 3H), 2.87–2.69 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.97, 160.96, 160.27, 158.65, 157.25, 155.68, 151.32, 140.24, 130.20, 129.34, 129.25, 128.54, 128.43, 128.03, 127.54, 127.15, 123.68, 122.61, 115.57, 115.42, 114.95, 114.40, 113.80, 113.48, 94.87, 54.92, 54.77, 52.52, 50.89, 50.26, 30.85.

Methyl 2,6-bis(2-thenyl)-1-(4-methoxyphenyl)-4-((4-methoxyphenyl)amino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**4l**) white solid. Mp: 210–212 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.44 (s, 1H), 7.23 (d, J = 5.0 Hz, 1H), 7.12 (d, J = 3.3 Hz, 1H), 7.07 (d, J = 5.0 Hz, 1H), 7.04–6.99 (m, 1H), 6.93 (t, J = 6.4 Hz, 5H), 6.82 (m, 3H), 6.72 (d, J = 9.0 Hz, 2H), 5.94 (s, 1H), 4.78 (t, J = 7.8 Hz, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 3.70 (s, 3H), 2.79 (d, J = 7.9 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.71 (d, J = 18.6 Hz), 157.72, 157.25, 156.18, 153.25, 151.43, 149.02, 148.15, 146.94, 143.99, 139.98, 130.53, 130.21, 127.11, 126.39, 125.87, 125.77, 125.56, 123.80, 123.72, 123.55, 123.51, 123.24, 122.86, 122.77, 118.42, 115.23, 113.89, 113.67, 113.57, 113.45, 96.24, 95.54, 60.01 56.21, 54.90, 54.80, 53.08, 52.88, 50.23, 36.26, 33.39.

Ethyl 2,6-bis(4-methoxyphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**4m**) white solid. Mp: 166–168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 1H), 7.23 (d, J = 8.5 Hz, 2H), 7.15–7.04 (m, 7H), 6.81 (m, 4H), 6.60 (t, J = 7.2 Hz, 1H), 6.53 (d, J = 8.2 Hz, 2H), 6.38–6.35 (m, 2H), 6.34 (s, 1H), 5.08 (d, J = 3.4 Hz, 1H), 4.44 (m, 1H), 4.32 (m, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 2.85 (dd, J = 15.0, 5.5 Hz, 1H), 2.75 (dd, J = 15.0, 2.4 Hz, 1H), 1.46 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.64, 158.07, 157.42, 155.51, 146.43, 137.40, 135.38, 134.05, 128.21, 127.06, 126.83, 125.07, 124.92, 115.41, 113.36, 112.93, 112.37, 97.80, 58.99, 56.90, 54.67, 54.60, 53.93, 33.12, 14.18.

Ethyl 2,6-bis(4-methphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**4n**) white solid. Mp: 228–230 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.29 (s, 1H), 7.20 (m, 2H), 7.11–7.04 (m, 11H), 6.58 (dd, J = 13.2, 5.9 Hz, 1H), 6.52 (d, J = 8.3 Hz, 2H), 6.41 (s, 1H), 6.33–6.24 (m, 2H), 5.11 (d, J = 4.2 Hz, 1H), 4.50–4.38 (m, 1H), 4.37–4.26 (m, 1H), 2.86 (dd, J = 15.0, 5.6 Hz, 1H), 2.76 (dd, J = 15.0, 2.3 Hz, 1H), 2.33 (s, 3H), 2.32 (s, 3H), 1.46 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.64, 155.43, 146.48, 140.45, 139.09, 137.40, 135.95, 135.10, 128.65, 128.62, 128.34, 128.28, 128.21, 128.14, 126.07, 125.92, 125.70, 125.10, 124.88, 115.52, 115.33, 112.29, 97.78, 58.98, 57.31, 54.27, 33.02, 20.46, 20.37, 14.16.

Ethyl 1,2,6-triphenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**4o**) white solid. Mp: 172–173 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.30 (s, 1H), 7.25 (m, 10H), 7.13–7.02 (m, 5H), 6.61 (t, J = 7.2 Hz, 1H), 6.53 (d, J = 8.3 Hz, 2H), 6.47 (s, 1H), 6.27 (dd, J = 7.3, 1.9 Hz, 2H), 5.15 (d, J = 3.8 Hz, 1H), 4.47 (dq, J = 10.8, 7.1 Hz, 1H), 4.33 (dq, J = 10.8, 7.1 Hz, 1H), 2.88 (dd, J = 15.1, 5.7 Hz, 1H), 2.77 (dd, J = 15.1, 2.3 Hz, 1H), 1.47 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.63, 155.44, 146.37, 143.44, 142.15, 137.29, 128.27, 128.20, 128.00, 127.61, 126.51, 126.02, 125.78, 125.65, 125.17, 125.04, 115.52, 112.34, 97.62, 59.06, 57.61, 54.49, 33.00, 14.18.

Ethyl 2,6-bis(4-fluorophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**4p**) white solid. Mp: 204–208 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.31 (s, 1H), 7.27 (dd, J = 8.4, 5.4 Hz, 2H), 7.17–7.05 (m, 7H), 6.95 (m, 4H), 6.63 (t, J = 7.3 Hz, 1H), 6.48 (d, J = 8.2 Hz, 2H), 6.39 (d, J = 8.0 Hz, 3H), 5.11 (d, J = 3.1 Hz, 1H), 4.45 (m, 1H), 4.32 (m, 1H), 2.83 (dd, J = 15.2, 5.6 Hz, 1H), 2.75 (dd, J = 15.2, 2.6 Hz, 1H), 1.45 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.07, 162.98, 162.52, 161.03, 160.57, 155.88, 146.67, 139.53 (d, J = 2.9 Hz), 138.14 (d, J = 3.0 Hz), 137.81, 129.01, 128.98, 128.17, 128.11, 127.96, 127.90, 125.86, 125.65, 116.62, 115.55, 115.38, 115.10, 114.93, 113.07, 98.12, 59.81, 57.35, 54.68, 33.81, 14.80.

Ethyl 2,6-bis(4-chlorophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**4q**) white solid. Mp: 230–232 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.29 (s, 1H), 7.26–7.21 (m, 6H), 7.19–7.03 (m, 8H), 6.64 (t, J = 7.3 Hz, 1H), 6.46 (d, J = 8.2 Hz, 2H), 6.40 (d, J = 7.3 Hz, 2H), 6.36 (s, 1H), 5.09 (d, J = 3.2 Hz, 1H), 4.44 (dq, J = 10.8, 7.1 Hz, 1H), 4.32 (dq, J = 10.8, 7.1 Hz, 1H), 2.78 (ddd, J = 17.8, 15.2, 4.1 Hz, 2H), 1.45 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.00, 155.82, 146.57, 142.54, 141.01, 137.76, 132.92, 132.18, 129.09, 129.04, 128.80, 128.44, 128.08, 127.83, 125.97, 125.71, 116.81, 113.05, 97.90, 59.89, 57.42, 54.81, 33.74, 14.82.

Ethyl 2,6-bis(4-fluorophenyl)-1-(4-methoxyphenyl)-4-((4-methoxyphenyl)amino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**4r**) white solid. Mp: 224–228 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.16 (s, 1H), 7.25–7.22 (m, 1H), 7.12–7.06 (m, 2H), 6.99–6.90 (m, 4H), 6.67 (t, J = 6.1 Hz, 4H), 6.42–6.38 (m, 2H), 6.35 (t, J = 6.0 Hz, 2H), 6.23 (s, 1H), 5.02–4.93 (m, 1H), 4.40 (ddd, J = 14.2, 9.0, 5.4 Hz, 1H), 4.33–4.23 (m, 1H), 3.75 (s, 3H), 3.67 (s, 3H), 2.73 (dd, J = 15.3, 5.6 Hz, 1H), 2.62 (dd, J = 15.3, 3.2 Hz, 1H), 1.41 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.22, 162.52, 160.57, 157.97, 156.63, 151.49, 141.26, 139.83, 138.68, 130.72,

128.42, 128.36, 128.20, 128.14, 127.75, 115.52, 115.35, 114.97, 114.88, 114.81, 114.60, 114.16, 97.03, 59.64, 57.30, 55.68, 55.47, 33.79, 14.81.

Conclusion

In summary, we have developed an efficient protocol to construct highly functionalized piperidines though employing catalytic amount of TMSI via one-pot multicomponent reaction of β-ketoester, aromatic aldehydes, and aromatic amines in methanol at room temperature. This novel method may have great potential in the synthesis field of highly functionalized piperidines because of the mild reaction conditions, simple operation procedure, superior atom-economy, and eco-friendly catalyst.

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