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BIS(1,3-DIMETHYLIMIDAZOLIDINONE) HYDROTRIBROMIDE (DITB) PROMOTED MULTICOMPONENT REACTION FOR THE SYNTHESIS OF HIGHLY FUNCTIONALIZED PIPERIDINES

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Abstract – A convenient and efficient method has been developed for the synthesis of highly functionalized piperidines via three-component, one-pot domino reaction of β -ketoesters, aromatic aldehydes, and anilines in the presence of catalytic amount of bis(1,3-dimethylimidazolidinone) hydrotribromide (DITB) in ethanol at room temperature.

INTRODUCTION

Highly functionalized piperidines are privileged scaffolds found in many natural alkaloids,¹ synthetic pharmaceuticals, and a wide variety of bioactive compounds² with anti-bacterial,³ anti-malarial,⁴ anti-inflammatory,⁵ anti-convulsant,⁶ and anti-hypertensive⁷ activities.

Recently, multicomponent reactions (MCRs) with various catalysts for the synthesis of highly functionalized piperidines have attracted more attentions due to its environmentally benign, atom economy, time-saving and free of protection-deprotection operation. Organic acids including picric acid,^{8a} tartaric acid,^{8b} citric acid,^{8c} PSSA,^{8d} oxalic acid,^{8e} CSA,^{8f} as well as Lewis acids such as Bi(NO₃)₃,^{9a} ZrOCl₂,^{9b} SbI₃,^{9c} InCl₃,^{9d} Ce(OTf)₄,^{9e} LaCl₃,^{9f} TiCl₂,^{9g} NiCl₂,^{9h} and Fe(NO₃)₃,⁹ⁱ as efficient catalysts for the synthesis of highly functionalized piperidines have been reported. In addition, nanopowder¹⁰ and graphene oxide¹¹ also have been used to promote the formation of these compounds. Despite the large number of reported catalysts mentioned above, many of the methods suffered from disadvantages such as the use of expensive reactants or catalysts, requiring excess amounts of reagents, use of toxic metals or volatile organic solvents, or harsh conditions, tedious work-up procedures. Hence, the development of a

facile and high-yielding environmentally benign protocol for one-pot multicomponent synthesis of densely functionalized piperidine scaffolds is still highly desired.

Very recently, Matsubara and co-workers developed a novel air stable bromination reagent, namely bis(1,3-dimethylimidazolidinone) hydrotribromide (DITB, Figure 1).¹² DITB is a complex of two 1,3-dimethylimidazolidinone (DMI) molecules and HBr_3 , which conveniently alternative to molecular bromine under bromination reactions. Previous literatures revealed that, bromodimethylsulfonium bromide (BDMS),¹³ tetrabutylammonium tribromide (TBATB),¹⁴ PEG-embedded KBr_3 ¹⁵ and Fe_2O_3 -BIM tribromide¹⁶ were efficient catalysts for the synthesis of functionalized piperidine scaffolds. With the information in hand, we speculate that DITB may be used to promote the formation of highly functionalized piperidines.

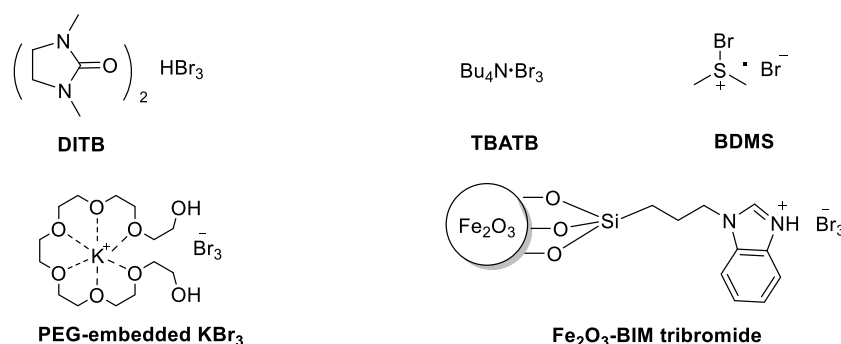
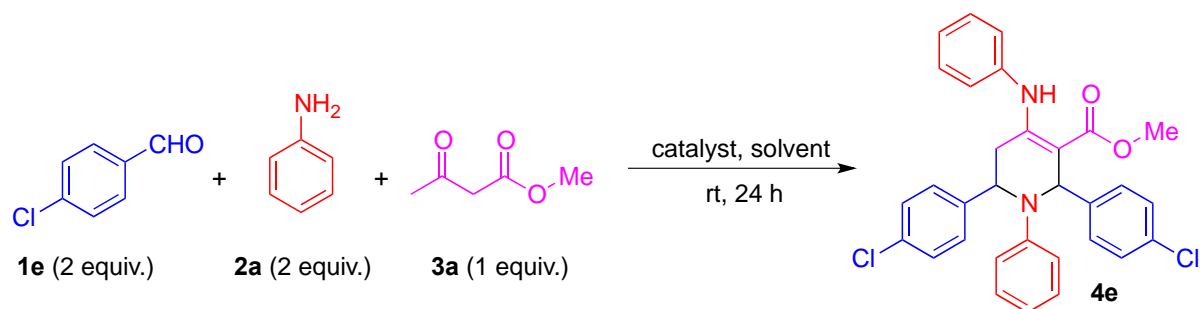


Figure 1. Structures of DITB, TBATB, BDMS, PEG-embedded KBr_3 and Fe_2O_3 -BIM tribromide

In continuation of our interests in developing novel eco-friendly and easy-to-handle synthesis methodology,¹⁷ herein we describe the preparation of densely functionalized piperidines *via* one-pot multicomponent reactions of β -ketoester, aldehyde and aniline catalyzed by DITB.¹⁸

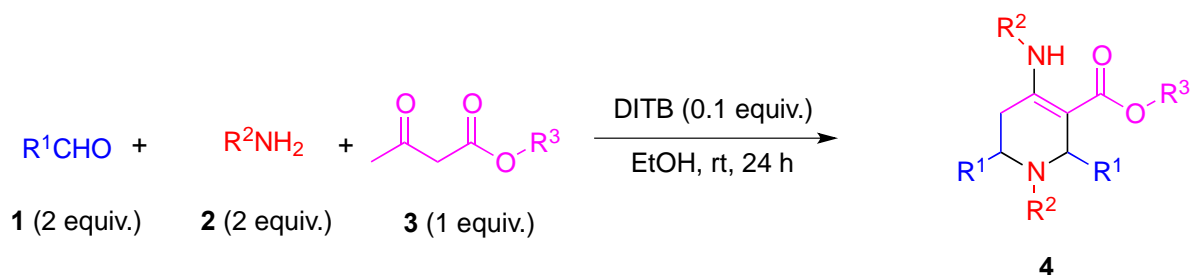
RESULTS AND DISCUSSION

p-Chlorobenzaldehyde (**1e**, 2 mmol, 2 equiv.), aniline (**2a**, 2 mmol, 2 equiv.) and methyl acetoacetate (**3a**, 1 mmol, 1 equiv.) were selected as substitutes for model reaction. It was found that EtOH was the best choice among the solvents we screened (Table 1, entries 1-5), which gave desired piperidine in 92% isolated yield. Increasing the amount of catalyst does not help to improve yield (Table 1, entry 6). While using less amount of catalyst (0.05 equiv., Table 1, entry 7), the yield dropped to 74%. In a blank experiment, i.e., performed the reaction without catalyst, no piperidine was observed (Table 1, entry 8). Other catalysts such as DBDMH, NBS, and TBAF were also screened, but gave only 76% yield (Table 1, entry 9) or trace products (Table 1, entries 10-11).

Table 1. Optimization of the reaction conditions

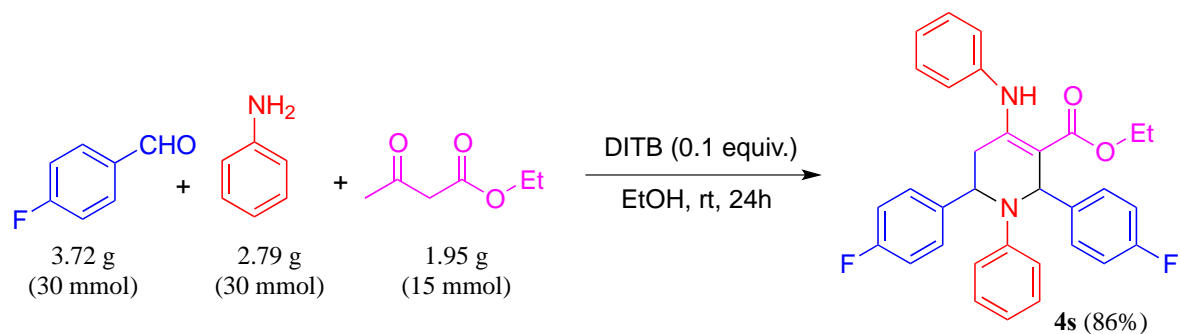
Entry	Solvent	Catalyst	Catalyst equiv.	Yield (%)
1	CH ₂ Cl ₂	DITB	0.1	39
2	THF	DITB	0.1	51
3	MeCN	DITB	0.1	68
4	MeOH	DITB	0.1	79
5	EtOH	DITB	0.1	92
6	EtOH	DITB	0.2	86
7	EtOH	DITB	0.05	74
8	EtOH	none	--	0
9	EtOH	DBDMH	0.1	76
10	EtOH	NBS	0.2	trace
11	EtOH	TBAF	0.2	trace

With the optimal reaction conditions in hand, the generality of the DITB promoted piperidine synthesis with a wide range of substrates was investigated (Table 2). A mixture of aniline, methyl acetoacetate, and DITB in EtOH were stirred for 30 min followed by the addition of aldehyde smoothly gave the desired piperidine (Table 2, entries 1-7). Substituted benzaldehydes bearing electron-donating (Table 2, entries 1, 3) or –withdrawing (Table 2, entries 4-5) groups worked well by this protocol. Fused- and heterocyclic-aromatic aldehydes also gave satisfactory results (Table 2, entries 6-7). However, aliphatic aldehydes such as *n*-hexanal and isobutyl aldehyde did not work by this method (results not shown in the Table). Replacing aniline with *p*-anisidine (with electron-donating group) or *p*-chloroaniline (with electron-withdrawing group), also gave good results (Table 2, entries 8-14). However, benzylamine afforded the corresponding piperidine in relatively lower yield (Table 2, entry 15). Other β-ketoester such as ethyl acetoacetate was also screened, which gave similar results comparing to its methylate analog (Table 2, entries 16-19).

Table 2. Synthesis of high functionalized piperidines under optimized condition

Entry	R ¹	R ²	R ³	Product	Isolated Yield (%)
1	4-MeOC ₆ H ₄	C ₆ H ₅	Me	4a	70
2	C ₆ H ₅	C ₆ H ₅	Me	4b	82
3	4-MeC ₆ H ₄	C ₆ H ₅	Me	4c	79
4	2-FC ₆ H ₄	C ₆ H ₅	Me	4d	89
5	4-ClC ₆ H ₄	C ₆ H ₅	Me	4e	92
6	1-Naphthyl	C ₆ H ₅	Me	4f	81
7	2-Thenyl	C ₆ H ₅	Me	4g	75
8	C ₆ H ₅	4-MeOC ₆ H ₄	Me	4h	67
9	2-FC ₆ H ₄	4-MeOC ₆ H ₄	Me	4i	76
10	2-Thenyl	4-MeOC ₆ H ₄	Me	4j	43
11	4-MeOC ₆ H ₄	4-ClC ₆ H ₄	Me	4k	75
12	C ₆ H ₅	4-ClC ₆ H ₄	Me	4l	82
13	4-FC ₆ H ₄	4-ClC ₆ H ₄	Me	4m	89
14	2-Thenyl	4-ClC ₆ H ₄	Me	4n	77
15	C ₆ H ₅	C ₆ H ₅ CH ₂	Me	4o	49
16	4-MeOC ₆ H ₄	C ₆ H ₅	Et	4p	70
17	4-MeC ₆ H ₄	C ₆ H ₅	Et	4q	84
18	C ₆ H ₅	C ₆ H ₅	Et	4r	68
19	4-FC ₆ H ₄	C ₆ H ₅	Et	4s	90

Finally, we performed the reaction on a gram scale (Scheme 1) and were pleased to find that the desired piperidine **4s** was obtained in 86% yield, which clearly demonstrates the preparative utility of this newly developed method.

**Scheme 1.** Scaleup of the reaction

In summary, we have developed an efficient protocol for the construction of highly functionalized piperidines by employing catalytic amount of DITB *via* one-pot multicomponent reaction of β -ketoesters, aromatic aldehydes, and various amines in ethanol at room temperature. The attractive features of this procedure are the mild reaction conditions, operational simplicity, superior atom-economy, and the use of eco-friendly catalyst.

EXPERIMENTAL

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. 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 (^1H NMR) spectra are reported in parts per million relative to the signal residual (CDCl_3 at 7.26 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 77.16 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 of piperidines (4a-4s)

A mixture of β -ketoester (1 mmol) and substituted aniline (2 mmol) in EtOH (10 mL) in the presence of DITB (47 mg, 0.1 mmol) was stirred for 30 min at room temperature, followed by the addition of aldehyde (2 mmol). The resulting mixture was continuously stirred until the completion of reaction. Then the reaction mixture was concentrated and the precipitate was filtered off and washed with EtOH (2 mL) to give pure products.

Methyl 2,6-bis(4-methoxyphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4a)^{8b}: white solid; mp 188–189 °C; IR (KBr): 2949, 2838, 1654, 1610, 1593, 1497, 1246, 1232, 1071, 1032, 758, 698 cm^{-1} ; ^1H 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 (125 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; ESI-MS m/z : 518.8 [M-H] $^-$.

Methyl 1,2,6-triphenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4b)^{8b}: white solid; mp 170–172 °C; IR (KBr): 3250, 3025, 2950, 2868, 1682, 1604, 1588, 1504, 1253, 1079, 748, 700 cm^{-1} ; ^1H 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 (125 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; ESI-MS m/z : 458.9 $[\text{M-H}]^-$.

Methyl 1-phenyl-4-(phenylamino)-2,6-di-*p*-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylate (4c)^{8b}: white solid; mp 210–212 °C; IR (KBr): 3251, 2946, 2869, 1658, 1603, 1587, 1505, 1248, 1078, 791, 747, 688 cm^{-1} ; ^1H 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 (125 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; ESI-MS m/z : 486.8 $[\text{M-H}]^-$.

Methyl 2,6-bis(2-fluorophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4d): white solid; mp 178–180 °C; IR (KBr): 2951, 2887, 1654, 1594, 1584, 12658, 1255, 1090, 761, 755, 749 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 10.15 (s, 1H), 7.26–6.95 (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), 2.93–2.87 (m, 2H); ^{13}C NMR (125 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; HRESI-MS calcd for $[\text{C}_{31}\text{H}_{26}\text{F}_2\text{N}_2\text{O}_2+\text{Na}]^+$ 519.1855, found 519.1853.

Methyl 2,6-bis(4-chlorophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4e)^{8b}: white solid; mp 220–222 °C; IR (KBr): 2948, 2862, 1660, 15907, 1496, 1488, 1260, 1248, 1071, 754, 698 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 11.97 (s, 1H), 10.25 (s, 1H), 7.26–7.01 (m, 28H), 6.73 (t, $J = 7.3$ Hz, 1H), 6.64 (t, $J = 7.3$ Hz, 1H), 6.51 (d, $J = 8.0$ Hz, 2H), 6.45 (d, $J = 8.2$ Hz, 2H), 6.40 (d, $J = 6.8$ Hz, 2H), 6.35 (s, 1H), 5.87 (s, 1H), 5.09 (d, $J = 3.1$ Hz, 1H), 5.01 (t, $J = 5.4$ Hz, 1H), 3.92 (s, 3H), 3.85 (s, 3H), 3.01 (dd, $J = 16.6, 5.7$ Hz, 1H), 2.82 (dd, $J = 15.2, 5.5$ Hz, 1H), 2.77–2.65 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.36, 169.74, 167.67, 155.37, 145.95, 145.83, 141.73, 140.29, 139.98, 139.77, 136.98, 132.29, 132.26, 132.19, 131.53, 128.41, 128.39, 128.19, 128.15, 127.81, 127.78, 127.74, 127.41, 127.37, 127.14, 125.41, 125.12, 118.68, 116.92, 116.14, 112.31, 100.85, 96.91, 57.02, 56.73, 55.30, 54.11, 51.31, 50.53, 35.89, 33.05; ESI-MS m/z : 527.6 $[\text{M-H}]^-$.

Methyl 2,6-di(naphthalen-1-yl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4f): white solid; mp 215–217 °C; IR (KBr): 3044, 2949, 1654, 1593, 1580, 1503, 1492, 1247, 1230, 1078, 1068, 796, 789, 774, 697 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 12.73 (s, 0.51H), 10.81 (s, 0.92H),

8.16–7.86 (m, 5.78H), 7.59 (m, 9.49H), 7.41–7.28 (m, 2.12H), 7.24–6.74 (m, 16.62H), 6.60 (s, 1H), 6.51 (m, 3H), 6.41 (d, $J = 7.9$ Hz, 2H), 6.21–6.15 (m, 1H), 5.41 (dd, $J = 9.2, 3.6$ Hz, 1H), 5.26–5.18 (m, 0.75H), 3.71 (s, 3H), 3.66 (s, 2.25H), 3.06 (m, 1.75H), 2.76 (dd, $J = 16.3, 3.6$ Hz, 1H), 2.52 (dd, $J = 17.5, 3.1$ Hz, 0.75H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.69, 171.87, 169.48, 157.96, 147.50, 147.40, 139.52, 138.42, 137.97, 136.12, 135.44, 134.40, 134.28, 133.58, 133.36, 132.91, 132.71, 132.08, 131.51, 128.95, 128.57, 128.55, 128.43, 128.38, 128.35, 128.21, 128.17, 128.01, 127.87, 126.19, 125.93, 125.76, 125.56, 125.42, 125.37, 125.19, 125.15, 125.07, 124.85, 125.80, 124.71, 124.62, 124.24, 123.72, 123.62, 121.79, 121.36, 98.65, 93.79, 58.53, 58.27, 52.53, 51.83, 51.49, 51.02, 28.75, 27.70; HRESI-MS calcd for $[\text{C}_{39}\text{H}_{32}\text{N}_2\text{O}_2+\text{Na}]^+$ 583.2356, found 583.2361.

Methyl 1-phenyl-4-(phenylamino)-2,6-di(thiophen-2-yl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4g)^{9b}: white solid; mp 220–222 °C; IR (KBr): 3065, 3035, 2940, 1655, 1614, 1596, 1580, 1496, 1275, 1253, 1070, 692 cm^{-1} ; ^1H 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 (125 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, 123.31, 118.64, 115.75, 112.75, 97.85, 58.90, 55.36, 50.42, 36.33; ESI-MS m/z : 470.6 $[\text{M}-\text{H}]^-$.

Methyl 1-(4-methoxyphenyl)-4-((4-methoxyphenyl)amino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (4h)^{9d}: white solid; mp 223–225 °C; IR (KBr): 3258, 2949, 2930, 2835, 1652, 1511, 1258, 1238, 1075, 700 cm^{-1} ; ^1H 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 (125 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; ESI-MS m/z : 520.8 $[\text{M}+\text{H}]^+$.

Methyl 2,6-bis(2-fluorophenyl)-1-(4-methoxyphenyl)-4-((4-methoxyphenyl)amino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4i): white solid; mp 202–204 °C; IR (KBr): 3265, 2947, 2835, 1652, 1511, 1266, 1231, 1073, 1040, 810, 756 cm^{-1} ; ^1H 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 (125 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; HRESI-MS calcd for $[\text{C}_{33}\text{H}_{30}\text{F}_2\text{N}_2\text{O}_4+\text{H}]^+$ 557.2246, found 557.2263.

Methyl 1-(4-methoxyphenyl)-4-((4-methoxyphenyl)amino)-2,6-di(thiophen-2-yl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4j)⁴: white solid; mp 210–212 °C; IR (KBr): 3242, 2942, 2830, 1654, 1611, 1508, 1242, 1043, 834, 821 cm^{-1} ; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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; ESI-MS *m/z*: 531.8 [M+H]⁺.

Methyl 1-(4-chlorophenyl)-4-((4-chlorophenyl)amino)-2,6-bis(4-methoxyphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4k)^{8b}: white solid; mp 199–200 °C; IR (KBr): 3235, 2947, 2838, 1662, 1605, 1586, 1498, 1251, 1073, 1034, 890, 795 cm^{-1} ; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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; ESI-MS *m/z*: 586.5 [M-H]⁻.

Methyl 1-(4-chlorophenyl)-4-((4-chlorophenyl)amino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (4l)^{9b}: white solid; mp 200–202 °C; IR (KBr): 3259, 3024, 2949, 2867, 1651, 1600, 1492, 1318, 1255, 1078, 800, 735, 698 cm^{-1} ; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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; ESI-MS *m/z*: 527.8 [M-H]⁻.

Methyl 1-(4-chlorophenyl)-4-((4-chlorophenyl)amino)-2,6-bis(4-fluorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4m)^{8c}: white solid; mp 175–177 °C; IR (KBr): 3257, 2957, 2868, 1653, 1602, 1505, 1493, 1315, 1255, 1229, 1076, 798 cm^{-1} ; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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; ESI-MS m/z : 562.7 [M-H]⁻.

Methyl 1-(4-chlorophenyl)-4-((4-chlorophenyl)amino)-2,6-di(thiophen-2-yl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4n)^{9b}: white solid; mp 215–216 °C; IR (KBr): 3264, 2949, 2870, 1655, 1606, 1504, 1491, 1261, 1078, 800, 690cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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; ESI-MS m/z : 540.7 [M-H]⁻.

Methyl 1-benzyl-4-(benzylamino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (4o): white solid; mp 127–131 °C; IR (KBr): 3268, 3027, 2929, 1650, 1596, 1449, 1254, 1224, 1068, 743, 698cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.70 (t, J = 6.1 Hz, 1H), 7.42–7.11 (m, 20H), 4.78 (s, 1H), 4.62 (m, 2H), 4.05 (dd, J = 11.6, 5.0 Hz, 1H), 3.46 (s, 3H), 3.41–3.31 (m, 2H), 2.77 (dd, J = 17.1, 11.7 Hz, 1H), 2.65 (dd, J = 17.1, 5.1 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 170.43, 158.16, 144.20, 140.88, 139.52, 138.30, 128.41, 128.33, 128.09, 127.57, 127.53, 126.94, 126.86, 126.69, 126.43, 126.20, 125.64, 88.36, 57.76, 51.76, 49.78, 49.08, 45.60, 24.47; HRESI-MS calcd for [C₃₃H₃₂N₂O₂+H]⁺ 489.2537, found 489.2538.

Ethyl 2,6-bis(4-methoxyphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4p)^{8b}: white solid; mp 166–168 °C; IR (KBr): 3243, 2931, 2863, 1653, 1647, 1588, 1577, 1566, 1500, 1173, 1069, 1039, 1027, 697cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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; ESI-MS m/z : 533.2 [M-H]⁻.

Ethyl 1-phenyl-4-(phenylamino)-2,6-di-*p*-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylate (4q)^{8c}: white solid; mp 228–230 °C; IR (KBr): 3228, 2981, 2870, 1650, 1592, 1500, 1371, 1328, 1255, 1070, 787, 750, 692cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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; ESI-MS m/z : 501.2 [M-H]⁻.

Ethyl 1,2,6-triphenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4r)^{8b}: white solid; mp 172–173 °C; IR (KBr): 3246, 2981, 2874, 1652, 1592, 1499, 1372, 1327, 1252, 1070, 750, 698cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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; ESI-MS m/z : 473.0 [M-H]⁻.

Ethyl 2,6-bis(4-fluorophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4s)^{9a}: white solid; mp 204–208 °C; IR (KBr): 3073, 2977, 2870, 1647, 1604, 15937, 1505, 1261, 1225, 1156, 864, 793, 744cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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; ESI-MS m/z : 508.8 [M-H]⁻.

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 18. Preparation of bis(1,3-dimethyl-2-imidazolidinone) hydrotribromide (DITB): Followed by Matsubara's protocol (*Tetrahedron*, 2019, **75**, 1398). DITB was obtained as orange crystalline solid. Mp 117-118 °C; ¹H NMR (500 MHz, CDCl₃) δ 2.99 (s, 12H, NCH₃), 3.67 (s, 8H, CH₂), 11.25 (bs, 1H, HBr); ¹³C NMR (125 MHz, CDCl₃) δ 32.23, 46.36, 161.50.