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Trityl chloride as an efficient organic catalyst for one-pot, five-component and diastereoselective synthesis of highly substituted piperidines

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Abstract Trityl chloride is used as an efficient organic catalyst for the one-pot, five-component and diastereoselective synthesis of highly substituted piperidines by means of reaction between aromatic aldehydes, amines and β-ketoesters in methanol at 50 °C. The structure as well as relative stereochemistry of products was confirmed by single X-ray crystallographic analysis. This homogeneous catalyst procedure includes some important aspects like the easy work-up, diastereoselectivity, simple and readily available precursors, inexpensive catalyst, relatively short reaction time, and good to high yields.

Keywords Trityl chloride · Piperidine · β-Ketoester · Aldehyde · Amine

Introduction

Synthesis of six-membered nitrogen heterocyclic compounds such as piperidine rings is very important because of their pharmacological and biological properties. The piperidines and their analogues exhibit diverse biological activities such as antihypertensive [1], antibacterial [2], anticonvulsant, and anti-inflammatory agents [3], farnesyltransferase inhibitors [4], norepinephrine reuptake inhibitor (CTDP 31, 446) [5], antipsychotic agent (MDL-100907) [6], and antidepressant drug [7]. Furthermore, substituted piperidines have been identified as an important class of therapeutic agents in the treatment of Parkinson's disease [8–10], prolactinoma [11], schizophrenia [12–14], influenza infection [15, 16], cancer metastasis [17–19], viral infections including AIDS [20, 21], obesity, and diabetes [22–24], and also play key

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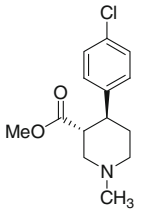
roles in many disease processes [25] (Fig. 1). These extensive investigations have resulted in the development of various synthetic methods for the synthesis of substituted piperidines [25–32].

Recently, the synthesis of highly functionalized piperidines has been reported using five-component reactions in the presence of $InCl_3$ [33, 34], bromodimethylsulfonium bromide (BDMS) [35], tetrabutylammonium tribromide (TBATB) [36], iodine [37], cerium ammonium nitrate [38], $ZrOCl_2 \cdot 8H_2O$ [39], picric acid [40], $BF_3 \cdot SiO_2$ [41], $Bi(NO_3)_3 \cdot 5H_2O$ [42], $LaCl_3 \cdot 7H_2O$ [43], VCl_3 [44], PEG-embedded KBr_3 [45], $Mg(HSO_4)_2$ [46], $Zn(HSO_4)_2$ [47], and $NiCl_2 \cdot 6H_2O$ [48] as catalyst. In addition, Misra and co-workers have reported the synthesis of highly functionalized piperidenes catalyzed by L-proline/TFA, and they also reported antimalarial activity of this class of compounds [49]. In view of the immense biological and pharmaceutical significance of these heterocycles, the introduction of an efficient method for the preparation of these compounds is still in demand.

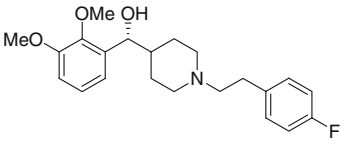
On the other hand, in recent years, organic catalysts have attracted considerable attention in a variety of synthetic reactions as catalyst because of their unique properties, such as the possibility to perform reactions for acid-sensitive substrates and selectivity [50–52]. In this respect, triarylmethyl chlorides get the broad attention of chemists from various fields, including synthesis of important compounds, bulky protective groups for amino and primary hydroxyl functional groups, and organic transformations [51–55]. Triarylmethyl chlorides are inexpensive and can be obtained commercially or easily prepared by the known procedure [56].

As a part of our continuing interest in the development of multi-component reactions for the synthesis of functionalized piperidine [57–60], we report here an efficient and convenient procedure for the synthesis of highly substituted piperidines



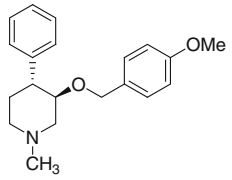
CTDP 31, 446

Norepinephrine reuptak Inhibitor[5]



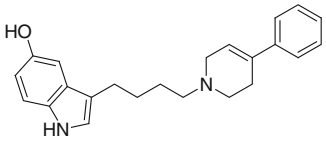
MDL-100907

Antipsychotic agent[6]



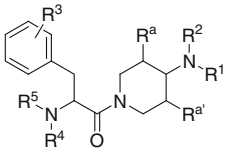
Femoxetine

Antidepressant drug[7]



Roxindole

Use for treatment of Parkinson's disease,[8,9] and schizophrnia[12,13]



Antiobesity and antidiabetic agent[24]

Fig. 1 Pharmaceutically active compounds containing piperidine framework

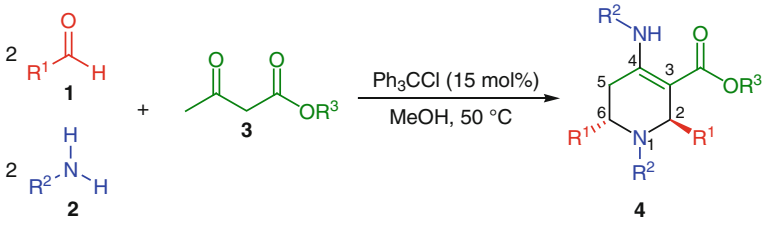
via a one-pot five-component reaction between aromatic aldehydes, amines and β-ketoesters catalyzed by trityl chloride (TrCl) in methanol at 50 °C (Scheme 1).

Results and discussion

Initially, the reaction of 4-methylbenzaldehyde, aniline and methyl acetoacetate in ethanol separately at ambient temperature was examined without any catalyst. This control experiment verified that the reaction did not proceed in the absence of a catalyst (Table 1, entry 1). When the reaction was carried out in the presence of trityl chloride (5 mol%) for 18 h, the corresponding highly substituted piperidine was obtained with 65 % yield. Encouraged by this result, we then focused on optimizing the reaction conditions. As shown in Table 1, the best result was obtained in the presence of 15 mol% of catalyst in methanol at 50 °C (Table 1, entry 10). The lower amounts of catalyst gave a low yield even after a long reaction time, and larger amounts of it did not affect the efficiency of this conversion. Furthermore, the effect of different solvents such as CH_3CN and H_2O was also investigated, and were found to be ineffective.

Therefore, the reactions of a series of substituted benzaldehydes, anilines and methyl- and/or ethyl-acetoacetate were carried out in the presence of 15 mol% of TrCl in methanol at 50 °C to afford the corresponding highly functionalized piperidines. The results are summarized in Table 2. In general, benzaldehydes containing an electron-deficient and/or electron-releasing group reacted efficiently with substituted anilines in the presence of β-ketoesters to give the corresponding piperidines in good to high yields. The low yield obtained in the reaction of benzyl amine, 4-methyl benzaldehyede and methyl acetoacetate is suggested to be because of the higher basicity of aliphatic amine compared to anilines (Table 2, entry 27). In addition, the reaction of propanal, as an aliphatic aldehyde, with aniline and methyl acetoacetate was checked under optimized conditions, but unfortunately did not provide the desired product (Table 2, entry 28).

All known products have been reported previously in the literature and were characterized by comparison of melting point, IR and NMR spectra with authentic samples. The structures of the products were fully characterized by melting points, elemental analyses, IR, ^{1}H and ^{13}C NMR, and mass spectra. For example, the mass spectrum of **4s** displayed a molecular ion peak (M^+) at $m/z = 524$, which is consistent with the proposed structure. The ^{1}H NMR spectrum of compound **4s**



Scheme 1 Synthesis of highly substituted piperidines **4**

Table 1 Optimization of the reaction conditions for the synthesis of highly substituted piperidine form the reaction between 4-methylbenzaldehyde, aniline and methyl acetoacetate

Entry	Catalyst (mol%)	Solvent/Conditions	Time (h)	Yield (%)[a]
1	–	EtOH/rt	24	–
2	5	EtOH/rt	18	65
3	7.5	EtOH/rt	14	69
4	10	EtOH/rt	14	74
5	12.5	EtOH/rt	14	76
6	15	EtOH/rt	12	78
7	20	EtOH/rt	12	78
8	25	EtOH/rt	12	77
9	15	MeOH/rt	8	79
10	15	MeOH/50 °C	5	81
11	15	MeOH/reflux	5	80
12	15	CH_3CN/rt	16	62
13	15	H_2O/rt	24	26
14	–	MeOH/50 °C	12	–

[a] Isolated yield

exhibited two singlets at δ 2.36 and 2.38 ppm for methyl groups and two doublets of doublets at 2.66 ppm ($J = 15.1$, 2.8 Hz) and 2.86 ppm ($J = 15.1$, 6.0 Hz) for methylene protons of the piperidin ring (H′-, H″-5). The protons of the methoxy group were observed at δ 3.95 ppm as a singlet. One of the methine protons of the piperidine ring (H-6) was observed as a doublet at δ 5.08 ($J = 4.0$ Hz) ppm and another methine proton (H-2) appeared as a singlet at δ 6.33 ppm. The aromatic protons resonance observed as multiplets at δ 6.25–7.20 ppm. The NH proton was observed at δ 10.17 ppm, which indicating intramolecular hydrogen bond formation with the vicinal carbonyl group. The ^{13}C NMR spectrum of compound **4s** showed 24 distinct resonances consistent with the piperidine structure. In the ^{13}C NMR spectrum of this compound, the C-5 carbon was observed at δ 33.6 ppm and C-2 was exhibited at δ 55.4 ppm. The C-6 and C-3 carbons were observed at δ 58.1 and 98.0 ppm, respectively. Also, the methyls and methoxy carbons were exhibited at δ 21.0, 21.1, and 51.0 ppm, respectively. The C-4 and aromatic carbons were observed at δ 113.6–160.7 ppm. In addition, the carbon of the carbonyl group was seen at δ 168.6 ppm. The structure as well as the relative stereochemistry of this class of compounds, for instance **4s**, was further elucidated by single crystal X-ray diffraction analysis (Fig. 2). As shown in Fig. 2, the relative *anti*-configuration of the product was confirmed. It is notable that, in the ^1H NMR spectra of the crude products, the corresponding *syn*-diastereomer was not identified, which confirmed the disatereoselectivity of the present protocol.

Crystal data and structure refinement for **4s** are presented in Table 3. Also, selected bond lengths, bond angles and torsion angles for **4s** were extracted from single X-ray crystallographic data and are exhibited in Table 4. It is noteworthy to mention that, on the basis of crystal X-ray analysis data, the piperidine ring adopted a boat conformation with some deviations (Scheme 2).

Table 2 The synthesis of highly substituted piperidine **4**

Entry	R^1	R^2	R^3	Product	Time (h)	Yield (%)[a]	M.p. (°C)	Lit. M.p. (°C)[b]
1	4-Me–C_6H_4	Ph	Me	**4a**	5	81	210–212	212–214 [35]
2	4-Me–C_6H_4	Ph	Et	**4b**	5.5	80	227–230	228–231 [37]
3	4-MeO–C_6H_4	Ph	Me	**4c**	5	79	189–190	187–188 [35]
5	3-Cl–C_6H_4	Ph	Me	**4d**	6	80	218–220	220–221 [38]
6	4-F–C_6H_4	Ph	Me	**4e**	4.5	74	176–179	180 [49]
7	3-NO_2–C_6H_4	Ph	Me	**4f**	9	41	178–181	182–183 [37]
8	Ph	Ph	Et	**4g**	5	75	171–172	174–175 [35]
9	Ph	4-Cl–C_6H_4	Et	**4h**	5	84	196–198	202 [49]
10	Ph	Ph	Me	**4i**	5	79	175–177	169–171 [35]
11	4-Me–C_6H_4	4-F–C_6H_4	Et	**4j**	4	79	183–185	183–185 [59]
12	4-Me–C_6H_4	4-Br–C_6H_4	Me	**4k**	6	80	227–229	229–230 [35]
13	4-Me–C_6H_4	3,4-diCl–C_6H_3	Et	**4l**	5	72	173–175	173–175 [59]
14	4-Me–C_6H_4	4-Me–C_6H_4	Me	**4m**	4	79	202–205	206–208 [37]
15	4-Br–C_6H_4	4-Cl–C_6H_4	Me	**4n**	4.5	73	160–162	160–163 [49]
16	4-MeO–C_6H_4	4-Br–C_6H_4	Me	**4o**	5	82	175–176	178 [49]
17	Ph	4-Me–C_6H_4	Et	**4p**	4	78	195–198	196–198 [42]
18	4-F–C_6H_4	4-Me–C_6H_4	Me	**4q**	4	79	200–202	200–202 [59]
19	3-Br–C_6H_4	Ph	Et	**4r**	5	83	163–165	164–167 [60]
20	4-Me–C_6H_4	4-F–C_6H_4	Me	**4s**	6	78	199–201	–
21	4-Me–C_6H_4	4-Cl–C_6H_4	Et	**4t**	5	81	218–220	–
22	4-Me–C_6H_4	4-Br–C_6H_4	Et	**4u**	5	76	234–236	–
23	3-Cl–C_6H_4	4-MeO–C_6H_4	Et	**4v**	5	70	167–169	167–170 [49]
24	4-Me–C_6H_4	4-Cl–C_6H_4	Me	**4w**	4	79	208–210	204–206 [60]
25	Ph	4-Me–C_6H_4	Et	**4x**	5.5	80	193–196	194–196 [60]
26	3-Me–C_6H_4	Ph	Et	**4y**	5	78	155–157	149–151 [60]
27	4-Me–C_6H_4	$PhCH_2$	Me	**4z**	24	37	169–171	172–173 [35]
28	Et	Ph	Me	–	24	—[c]	–	–

[a] Isolated yield

[b] References to known products in the literature

[c] No reaction

As reported in the literature [36–38, 41, 42, 57–60], a possible mechanism for the formation of piperidine **4** is shown in Scheme 3. Amine **2** reacts with aromatic aldehyde **1** and *β*-ketoester **3** in the presence of TrCl to give imine **5** and enamine **6**, respectively. The reaction between imine **5** and enamine **6** produces intermediate **7**, which reacts with another aldehyde **1** to afford intermediate **8**. Then, intermediate **8** is converted to intermediate **9**, which immediately undergoes an intramolecular Mannich-type reaction to give intermediate **10**. Finally, tautomerization of intermediate **10** gives the desired piperidine **4**.

To show the merit and applicability of TrCl in comparison with the reported catalysts, we compared results of these catalysts for the synthesis of highly

functionalized piperidine derivatives **4a** and **4i**, in Table 5. As shown in Table 5, TrCl can act as an effective and efficient catalyst with respect to reaction times and yield of products.

Experimental

General procedure for synthesis of highly substituted piperidine **4a–y**

First, a solution of aromatic amine (2 mmol) and β-ketoester (1 mmol) in methanol (5 mL) was stirred for 30 min in the presence of TrCl (15 mol%) at ambient temperature. Next, the aromatic aldehyde (2 mmol) was added and the reaction mixture was stirred at 50 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature. The thick precipitate was filtered off and washed with ethanol (3 × 2 mL) to give the pure product. Physical and spectral data of selected products are represented below.

*Methyl 1,2,5,6-tetrahydro-1-phenyl-4-(phenylamino)-2,6-dip-tolylpyridine-3-carboxylate (**4a**)*

White solid. (400 MHz, $CDCl_3$) δ (ppm): 2.25 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.75 (dd, 1H, J = 15.2, 2.4 Hz, H′-5), 2.84 (dd, 1H, J = 15.2, 5.6 Hz, H″-5), 3.93 (s, 3H, OCH_3), 5.09 (d, 1H, J = 3.1 Hz, H-6), 6.30 (d, 2H, J = 8.0 Hz, ArH), 6.37 (s, 1H, H-2), 6.48 (d, 2H, J = 8.8 Hz, ArH), 6.60 (t, 1H, J = 7.2 Hz, ArH), 6.99–7.12 (m, 11H, ArH), 7.20 (d, 2H, J = 8.0 Hz, ArH), 10.27 (s, 1H, NH).

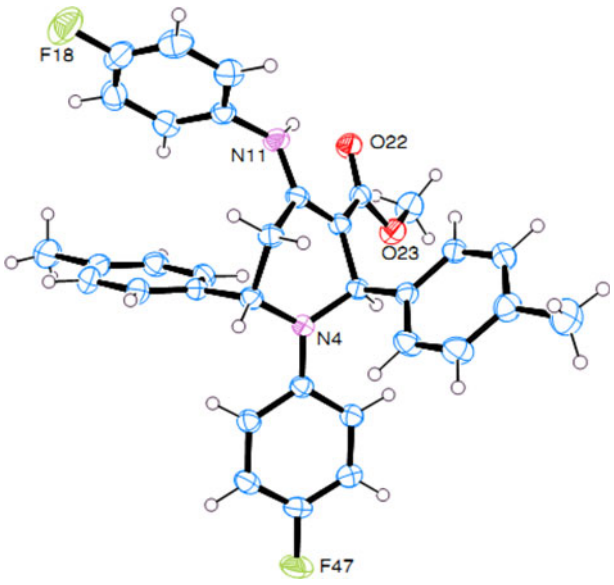


Fig. 2 ORTEP representation of the X-ray structure of piperidine **4s**

Table 3 Crystallographic data and structure refinement for compound **4s**

Empirical formula	$C_{33}H_{30}F_2N_2O_2$
Formula weight	524.61
Crystal system	Triclinic
Space group	$P\bar{1}$
a (Å)	9.7029(2)
b (Å)	11.1684(3)
c (Å)	13.9443(2)
α (°)	110.6790(14)
β (°)	100.5434(14)
γ (°)	96.1495(12)
V (Å^3)	1,365.42(5)
Z	2
D_x (Mg m^{-3})	1.276
μ (mm^{-1})	0.09
$T_{min/max}$	0.885/0.995
Crystal dimensions (mm)	0.51 × 0.37 × 0.06
$\theta_{max/min}$ (°)	27.5/2.7
Measured reflections	44,457
Independent reflections	6,253
Reflections [$I > 2\sigma(I)$]	5,000
R_{int}	0.063
Parameters/restraints	355/0
$R[F^2 > 2\sigma(F^2)]$	0.043
$wR(F^2)$	0.105
S	0.99
$(\Delta/\sigma)_{max}$	0.001
$\Delta\rho_{max/min}$ (e Å^{-3})	0.27/−0.27

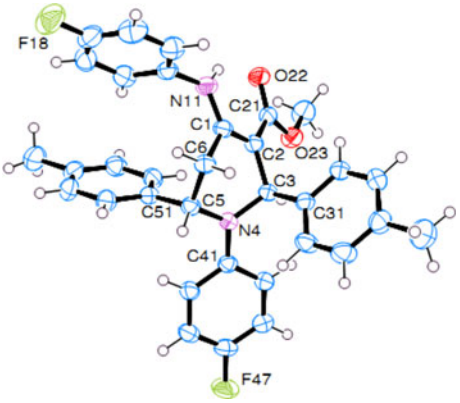
*Methyl 2,6-bis(4-fluorophenyl)-1,2,5,6-tetrahydro-1-phenyl-4-(phenylamino)pyridine-3-carboxylate (**4e**)*

Withe solid. (400 MHz, $CDCl_3$) δ (ppm): 2.75 (dd, 1H, J = 15.1, 2.0 Hz, H′-5), 2.87 (dd, 1H, J = 15.1, 5.6 Hz, H″-5), 3.95 (s, 3H, OCH_3), 5.11 (br s, 1H, H-6), 6.36–6.40 (m, 2H, ArH), 6.41 (s, 1H, H-2), 6.46–6.50 (m, 2H, ArH), 6.65 (t, 1H, J = 7.2 Hz, ArH), 6.90–7.24 (m, 13H, ArH), 10.29 (s, 1H, NH).

*Methyl 4-(4-chlorophenylamino)-2,6-bis(4-bromophenyl)-1-(4-chlorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (**4n**)*

White solid. (400 MHz, $CDCl_3$) δ (ppm): 2.73 (dd, 1H, J = 15.1, 2.2 Hz, H′-5), 2.85 (dd, 1H, J = 15.2, 5.6 Hz, H″-5), 3.95 (s, 3H, OCH_3), 5.13 (br s, 1H, H-6), 6.28 (d, 2H, J = 7.0 Hz, ArH), 6.36 (s, 1H, H-2), 6.45 (d, 2H, J = 6.9 Hz, ArH), 6.99–7.23 (m, 12H, ArH), 10.18 (s, 1H, NH).

Table 4 Selected bond lengths (Å), bond angles (°) and torsion angles (°) in piperidine structure **4s**

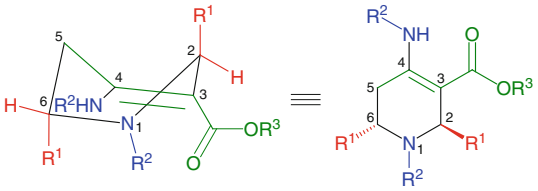


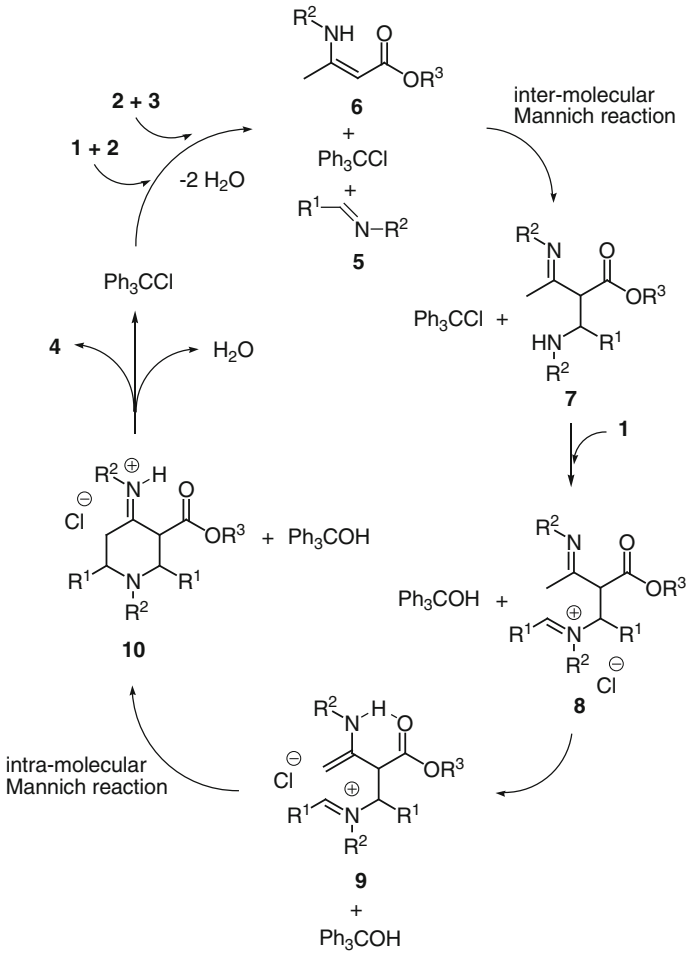
Entry	Bond	Length (Å)
1	C1–C2	1.3662(17)
2	C2–C3	1.5165(16)
3	C3–N4	1.4731(15)
4	N4–C5	1.4589(15)
5	C5–C6	1.5433(17)
6	C6–C1	1.5010(16)

Entry	Atom1	Atom2	Atom3	Angle (°)
1	C2	C1	C6	115.70(10)
2	C1	C2	C3	117.22(10)
3	C2	C3	N4	110.25(10)
4	C3	N4	C5	118.98(9)
5	N4	C5	C6	109.59(10)
6	C5	C6	C1	109.06(10)

Entry	Atom1	Atom2	Atom3	Atom4	Angle (°)
1	C1	C2	C3	N4	45.4(2)
2	C1	C6	C5	N4	55.5(1)
3	C1	C6	C5	C51	−70.0(1)
4	C2	C1	C6	C5	−49.4(2)
5	C2	C3	N4	C5	−36.6(1)
6	C3	N4	C5	C6	−12.3(1)
7	C3	C2	C1	C6	−1.8(2)
8	C5	C6	C1	N11	128.1(1)
9	C6	C1	C2	C21	171.7(1)

Scheme 2 The boat conformation of piperidine **4**





Scheme 3 Proposed reaction mechanism for synthesis of highly substituted piperidines **4**

*Ethyl 4-(p-tolylamino)-1,2,5,6-tetrahydro-2,6-diphenyl-1-p-tolylpyridine-3-carboxylate (**4p**)*

White solid. (400 MHz, $CDCl_3$) δ (ppm): 1.48 (t, 3H, $J = 7.0$ Hz, $OCH_2\underline{CH_3}$), 2.19 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.75 (dd, 1H, $J = 15.1$, 2.4 Hz, H′-5), 2.83 (dd, 1H,

Table 5 Comparison of TrCl with reported catalysts for the synthesis of highly substituted piperidine derivatives

Compound	Catalyst/conditions	Catalyst amount (mol %)	Time (h)	Yield (%)	Ref.
4a	$InCl_3/CH_3CN$, r.t.	33	24	50	[33]
	BDMS/CH_3CN, r.t.	10	3	80	[35]
	TBATB/EtOH, r.t.	10	8	78	[36]
	I_2/MeOH, r.t.	10	8	84	[37]
	CAN/CH_3CN, r.t.	15	22	85	[38]
	$ZrOCl_2{\cdot}8H_2O$/EtOH, reflux	20	–	–	[39]
	p-TsOH·H_2O/EtOH, r.t.	63	7	89	[55]
	$BF_3{\cdot}SiO_2$/MeOH, 65 °C	15	–	–	[41]
	$Bi(NO_3)_3{\cdot}5H_2O$/EtOH, r.t.	10	18	73	[42]
	L-proline/THF/CH_3CN, 20–30 °C	20	–	–	[49]
	TrCl/MeOH, 50 °C	15	5	81	—[a]
4i	$InCl_3/CH_3CN$, r.t.	33	24	60	[33]
	BDMS/CH_3CN, r.t.	10	3	75	[35]
	TBATB/EtOH, r.t.	10	24	74	[36]
	I_2/MeOH, r.t.	10	8	81	[36]
	CAN/CH_3CN, r.t.	15	20	82	[38]
	$ZrOCl_2{\cdot}8H_2O$/EtOH, reflux	20	3.5	80	[39]
	p-TsOH·H_2O/EtOH, r.t.	63	10	78	[55]
	$BF_3{\cdot}SiO_2$/MeOH, 65 °C	15	9	78	[41]
	$Bi(NO_3)_3{\cdot}5H_2O$/EtOH, r.t.	10	12	81	[42]
	L-proline/THF/CH_3CN, 20–30 °C	20	17	70	[49]
	TrCl/MeOH, 50 °C	15	5	79	–[a]

[a] This work

$J = 15.1, 5.2$ Hz, H″-5), 4.33–4.40 (m, 1H, OCH_aH_b), 4.48–4.55 (m, 1H, OCH_aH_b), 5.14 (d, 1H, $J = 2.8$ Hz, H-6), 6.19 (d, 2H, $J = 7.8$ Hz, ArH), 6.41 (d, 2H, $J = 8.0$ Hz, ArH), 6.43 (s, 1H, H-2), 6.90–7.17 (m, 7H, ArH), 7.21–7.36 (m, 7H, ArH), 10.24 (s, 1H, NH).

*Methyl 4-(4-fluorophenylamino)-1-(4-fluorophenyl)-1,2,5,6-tetrahydro-2,6-di-p-tolylpyridine-3-carboxylate (**4s**)*

White solid. mp: 199–201 °C. IR (KBr) $v = 3255$ (NH), 1649 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.36 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.66 (dd, 1H, $J = 15.1$, 2.8 Hz, H′-5), 2.86 (dd, 1H, $J = 15.1$, 6.0 Hz, H″-5), 3.95 (s, 3H, OCH_3), 5.08 (d, 1H, $J = 4.0$ Hz, H-6), 6.25–6.28 (m, 2H, ArH), 6.33 (s, 1H, H-2), 6.43–6.48 (m, 2H, ArH), 6.77–6.84 (m, 4H, ArH), 7.05–7.20 (m, 8H, ArH), 10.17

(s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 21.0 (CH_3), 21.1 (CH_3), 33.6 (C-5), 51.0 (OCH_3), 55.4 (C-2), 58.1 (C-6), 98.0 (C-3), 113.6 (d, $J = 7.0$ Hz), 115.2 (d, $J = 22.0$ Hz), 115.6 (d, $J = 22.0$ Hz), 126.4 (d, $J = 23.0$ Hz), 128.0 (d, $J = 8.0$ Hz), 129.0, 129.4, 133.9 (d, $J = 3.0$ Hz), 136.0, 136.9, 139.7, 140.6, 143.5, 155.0 (d, $^1J_{CF} = 233.0$ Hz), 156.2 (C-4), 160.7 (d, $^1J_{CF} = 244.0$ Hz), 168.6 (C=O). MS (EI, 70 eV) *m/z* (%): 524 (M^+, 16), 465 (6), 433 (100), 414 (8), 401 (18), 310 (61), 296 (51), 278 (22), 212 (66), 115 (23), 95 (41), 59 (14). Anal. Calcd for $C_{33}H_{30}F_2N_2O_2$: C, 75.55; H, 5.76; N, 5.34. Found: C, 75.82; H, 5.80; N, 5.39.

Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 864008 for **4s**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk), or via www.ccdc.cam.ac.uk/datarequest/cif.

*Ethyl 4-(4-chlorophenylamino)-1-(4-chlorophenyl)-1,2,5,6-tetrahydro-2,6-di-p-tolylpyridine-3-carboxylate (**4t**)*

White solid. mp: 218–220 °C. IR (KBr) $v = 3228$ (NH), 1645 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.49 (t, 3H, $J = 6.8$ Hz, $OCH_2\underline{CH_3}$), 2.35 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.73 (d, 1H, $J = 14.4$ Hz, H′-5), 2. 88 (dd, 1H, $J = 15.2$, 5.6 Hz, H″-5), 4.31–4.39 (m, 1H, OCH_aH_b), 4.45–4.51 (m, 1H, OCH_aH_b), 5.10 (d, 1H, $J = 3.2$ Hz, H-6), 6.22 (d, 2H, $J = 8.0$ Hz, ArH), 6.36 (s, 1H, H-2), 6.46 (d, 2H, $J = 8.8$ Hz, ArH), 7.01–7.21 (m, 12H, ArH), 10.27 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.7 ($OCH_2\underline{CH_3}$), 21.0 (CH_3), 21.1 (CH_3), 33.5 (C-5), 55.1 (C-2), 58.0 (C-6), 59.8 ($O\underline{CH_2}CH_3$), 98.9 (C-3), 114.0, 121.0, 126.2, 126.4, 126.9, 128.7, 128.9, 129.0, 129.4, 131.2, 136.1, 136.5, 137.0, 139.2, 140.3, 145.6, 155.3 (C-4), 168.1 (C=O). MS (EI, 70 eV) *m/z* (%): 571 (M^+, 2), 570 (4), 479 (22), 439 (20), 299 (21), 228 (39), 105 (32), 91 (63), 77 (31), 55 (100). Anal. Calcd for $C_{34}H_{32}Cl_2N_2O_2$: C, 61.45; H, 5.64; N, 4.93. Found: C, 61.67; H, 5.75; N, 4.96.

*Ethyl 4-(4-bromophenylamino)-1-(4-bromophenyl)-1,2,5,6-tetrahydro-2,6-di-p-tolylpyridine-3-carboxylate (**4u**)*

White solid. mp: 234–236 °C. IR (KBr) $v = 3310$ (NH), 1652 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.49 (t, 3H, $J = 6.8$ Hz, $OCH_2\underline{CH_3}$), 2.35 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.74 (d, 1H, $J = 15.2$ Hz, H′-5), 2.88 (dd, 1H, $J = 15.2$, 5.6 Hz, H″-5), 4.33-4.39 (m, 1H, OCH_aH_b), 4.45–4.51 (m, 1H, OCH_aH_b), 5.09 (d, 1H, $J = 3.6$ Hz, H-6), 6.17 (d, 2H, $J = 8.0$ Hz, ArH), 6.35 (s, 1H, H-2), 6.42 (d, 2H, $J = 8.8$ Hz, ArH), 7.05–7.24 (m, 12H, ArH), 10.26 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.7 ($OCH_2\underline{CH_3}$), 21.0 (CH_3), 21.2 (CH_3), 33.4 (C-5), 55.0 (C-2), 58.1 (C-6), 59.9 ($O\underline{CH_2}CH_3$), 99.0 (C-3), 108.2, 114.5, 118.9, 126.2, 126.4, 127.2, 129.0, 129.4, 131.5, 131.9, 136.1, 137.0, 139.1, 140.2, 146.0, 155.2 (C-4), 168.1 (C=O); MS (EI, 70 eV) *m/z* (%): 664 (M^{+4}, 13), 662 (M^{+2}, 25), 660 (M^+, 12), 587 (10), 569 (48), 488 (24), 386 (60), 272 (100), 312 (51), 245 (40), 105

(48), 91 (49), 77 (28), 55 (50). Anal. Calcd for $C_{34}H_{32}Br_2N_2O_2$: C, 61.83; H, 4.88; N, 4.24. Found: C, 61.99; H, 4.93; N, 4.39.

*Methyl 1-benzyl-4-(benzylamino)-1,2,5,6-tetrahydro-2,6-dip-tolylpyridine-3-carboxylate (**4z**)*

A mixture of benzyl amine (2 mmol) and methyl acetoacetate (1 mmol) in methanol (5 mL) was stirred for 30 min in the presence of TrCl (15 mol%) at ambient temperature. Next, the 4-methyl benzaldehyde (2 mmol) was added and the reaction mixture was stirred at 50 °C. After completion of the reaction (as monitored by TLC), the reaction mixture was cooled to ambient temperate and the solvent was evaporated under reduced pressure. Ethyl acetate (20 mL) was added and washed with H_2O and then brine, and dried with anhydrous Na_2SO_4. The filtrate was concentrated and purified by silica gel column chromatography in ethyl acetate: *n*-hexane (40:60) as eluent to give the piperidine **4z**. Light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.29 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.63 (dd, 1H, $J = 17.2$, 5.6 Hz, H′-5), 2.74 (dd, 1H, $J = 17.2$, 11.6 Hz, H″-5), 3.31 (d, 1H, $J = 13.5$ Hz, NCH_aH_b), 3.36 (d, 1H, $J = 13.5$ Hz, NCH_aH_b), 3.48 (s, 3H, OCH_3), 4.05 (dd, 1H, $J = 11.6$, 5.6 Hz, H-6), 4.56 (dd, 1H, $J = 15.6$, 6.0 Hz, $NHCH_aH_b$), 4.64 (dd, 1H, $J = 15.6$, 6.2 Hz, $NHCH_aH_b$), 4.73 (s, 1H, H-2), 7.08–7.24 (m, 9H, ArH), 7.29–7.38 (m, 9H, ArH), 9.65 (t, 1H, $J = 6.0$ Hz, NH).

Conclusion

In summary, the use of trityl chloride as an efficient organic catalyst is reported for the synthesis of highly substituted piperidines via a one-pot five-component reaction between aromatic aldehydes, amines and *β*-ketoesters in methanol at 50 °C in good to high yields. This methodology offered several advantages such as mild reaction conditions, simplicity in operation, diastereoselectivity, and simple and readily available precursors, which make it a useful and attractive process for the synthesis of these important compounds.

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