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# TiCl<sub>2</sub>·2H<sub>2</sub>O catalyzed one-pot synthesis of highly functionalized tetrahydropiperidines and evaluation of their antimicrobial activities

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**Abstract:** One-pot condensation reaction of ethyl acetoacetate, various substituted benzaldehydes and anilines in the presence of TiCl<sub>2</sub>·2H<sub>2</sub>O yields highly functionalized tetrahydropiperidines. Atom economy, efficiency, and short reaction times are the advantages of the method, which is carried out under mild conditions using easily accessible and inexpensive chemicals. The antimicrobial activity of the synthesized products was evaluated against three Gram-positive and three Gram-negative bacteria, a yeast and a fungus strain using disc diffusion and minimum inhibitory concentration methods.

**Keywords:** antibacterial activity; multicomponent reaction; TiCl<sub>2</sub>·2H<sub>2</sub>O; tetrahydropiperidine.

## Introduction

In multicomponent reactions (MCRs), three or more different starting materials undergo a reaction to form diverse complex molecules in a one-pot strategy with reducing waste, good efficiency, high selectivity, time saving, and high safety [1–3]. Tetrahydropiperidine and their derivatives are an important class of heterocyclic molecules found in numerous natural products and biologically active compounds [4–9]. They have also shown

biological properties such as antihypertensive [10], antibacterial [11], anti-inflammatory [12], and antimalarial activity [13]. Tetrahydropiperidines have also been utilized as useful synthetic precursors for the preparation of other compounds. Various methods have been developed for the synthesis of functionalized piperidines in the presence of catalysts such as L-proline/TFA [13], InCl<sub>3</sub> [14], 1-methyl-2-oxopyrrolidinium hydrogen sulfate ([Hpyro][HSO<sub>4</sub>]) [15], tetrabutylammonium tribromide (TBATB) [7], ZrOCl<sub>2</sub>·8H<sub>2</sub>O [16], Bi(NO<sub>3</sub>)<sub>3</sub>·5H<sub>2</sub>O [17], SPINOL-phosphoric acids [18], BF<sub>3</sub>·SiO<sub>2</sub> [19], trityl chloride (Ph<sub>3</sub>CCl) [20], FeCl<sub>3</sub>/SiO<sub>2</sub> nanoparticles [21], cerium ammonium nitrate (CAN) [22], molecular iodine (I<sub>2</sub>) [23], and picric acid [24]. Despite the large number of reported catalysts for the synthesis of functionalized piperidines, many of the methods suffer from disadvantages such as long reaction times, need for excess amounts of the reagent, low yields, use of toxic or expensive reagents, tedious work-up procedures, and high temperature conditions. Therefore, there is a need for alternative methods that avoids these problems. In continuation of our interest in developing protocols for the synthesis of heterocyclic compounds [25, 26], herein we report TiCl<sub>2</sub>·2H<sub>2</sub>O as a new catalyst for the fast, facile, and efficient synthesis of highly functionalized piperidine derivatives by the direct condensation of a variety of anilines with aryl aldehydes and ethyl acetoacetate under mild reaction conditions (Scheme 1).

## Results and discussion

Initially, in order to find an efficient catalyst, the model reaction of benzaldehyde (2 mmol), aniline (2 mmol), and ethyl acetoacetate (1 mmol) in the presence of various potential catalysts in ethanol at ambient temperature was studied. The results are summarized in Table 1. As can be seen, the best result was obtained using TiCl<sub>2</sub>·2H<sub>2</sub>O.

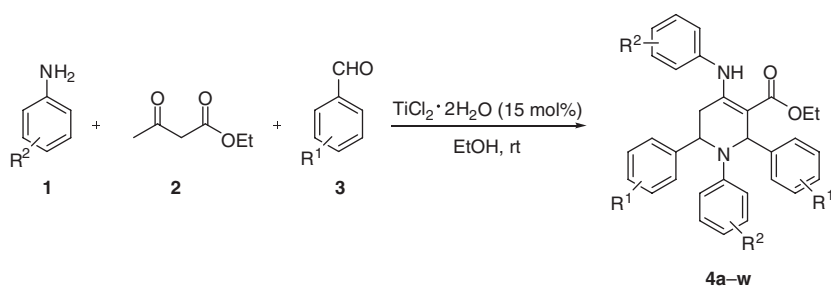
Then, the model reaction was optimized by using several solvents. The results presented in Table 2 show

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**Scheme 1** Synthesis of compounds **4a–w**. For definition of the substituents  $R^1$  and  $R^2$ , see Table 3.

**Table 1** Synthesis of piperidine **4a**<sup>a</sup> in the presence of various catalysts.

Entry	Catalyst (10 mol%)	Time (h)	Yield (%)
1	$\text{Sr}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$	24	10
2	$\text{NaH}_2\text{PO}_4$	24	Trace
3	$\text{Al}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$	20	25
4	$(\text{NH}_4)_3\text{PMo}_{12}\text{O}_{40} \cdot 6\text{H}_2\text{O}$	20	40
5	$\text{Co}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$	18	45
6	$\text{IrCl}_3 \cdot 3\text{H}_2\text{O}$	12	62
7	$\text{TiCl}_2 \cdot 2\text{H}_2\text{O}$	7	73

<sup>a</sup>Experimental conditions: benzaldehyde (2 mmol), aniline (2 mmol), and ethyl acetoacetate (1 mmol) in ethanol (5 mL) at room temperature.

**Table 2** The effect of different solvents and different amounts of  $\text{TiCl}_2 \cdot 2\text{H}_2\text{O}$  on the yield of **4a** at room temperature.

Entry	Solvent	Catalyst (mol%)	Time (h)	Yield (%)
1	Neat	15	4	47
2	MeOH	15	4	85
3	$\text{CH}_3\text{CN}$	15	8	76
4	EtOAc	15	12	40
5	$\text{H}_2\text{O}$	15	20	–
6	$\text{CH}_2\text{Cl}_2$	15	20	Trace
7	EtOH	15	4	90
8	EtOH	–	18	–
9	EtOH	5	10	55
10	EtOH	10	7	73
11	EtOH	20	4	88

that EtOH is the solvent of choice. Running the synthesis of model compound **4a** in the absence of solvent leads to a 47% yield at room temperature (Table 2, entry 1).

Different molar ratios of the catalyst were also investigated. The best result was obtained in the presence of 15 mol%  $\text{TiCl}_2 \cdot 2\text{H}_2\text{O}$  in EtOH at room temperature (Table 2, entry 7). An increase in the amount of catalyst does not improve the yield and in its absence no product is obtained even after 18 h (Table 2, entries 8–11).

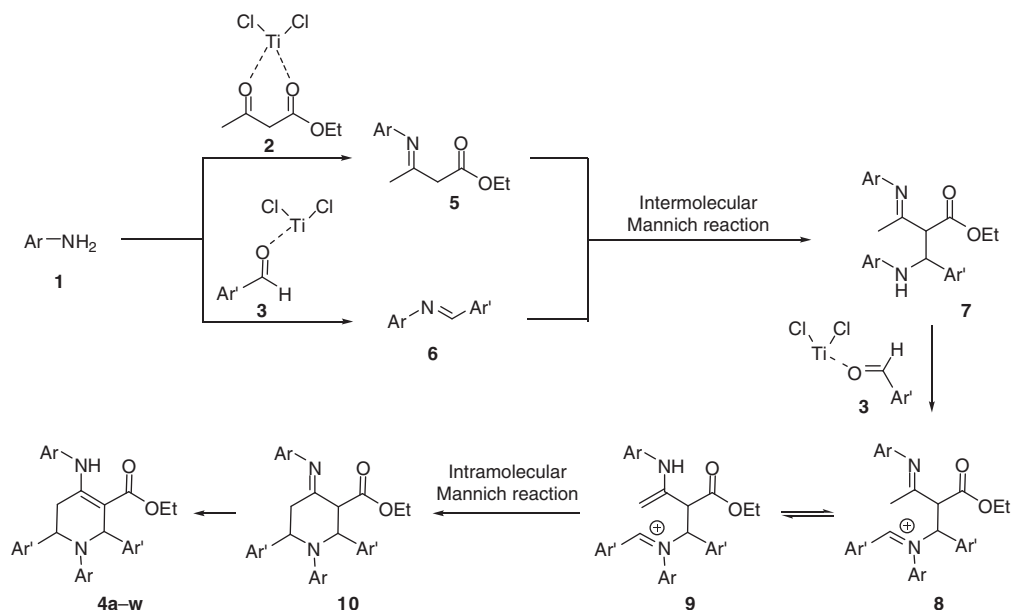
To explore the scope and substrate limitations of the reaction, various substituted benzaldehydes and anilines were allowed to react with ethyl acetoacetate under the optimized conditions. The results are summarized in Table 3. The method is efficient and superior in comparison with the reported literature preparations. Various derivatives were obtained in relatively high yields. The electron withdrawing or electron donating nature of the aryl group affects the reaction rate, but no clear substitution effect on the yield is observed. The structures of the synthesized products were identified by comparison of their spectroscopic data and melting points with those of literature reports. The structures of new compounds **4j** and **4s** were confirmed by IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, mass spectrometry, and elemental analysis data.

A plausible mechanism for the discussed synthesis is shown in Scheme 2. Initially, the reaction of arylamine **1** and ethyl acetoacetate **2** gives the  $\beta$ -enaminone **5** in the presence of  $\text{TiCl}_2 \cdot 2\text{H}_2\text{O}$  [27]. In a similar way, condensation of arylamine **1** with arylaldehyde **3** generates the corresponding imine **6**. Then, the intermolecular Mannich reaction of  $\beta$ -enaminone **5** with the imine **6** activated by  $\text{TiCl}_2 \cdot 2\text{H}_2\text{O}$  affords the intermediate product **7** [27]. The reaction of **7** with the second activated molecule of arylaldehyde produces the intermediate compound **8**. Then, **8** undergoes tautomerization to **9** which is stabilized by intramolecular hydrogen bond. Finally, the intramolecular Mannich-type reaction of **9** generates the intermediate product **10** which is a direct precursor to the final product **4a–w** [17].

The antimicrobial activity evaluations of selected compounds **4** against three Gram-positive containing (*Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Bacillus subtilis*) and three Gram-negative (*Klebsiella pneumoniae*, *Escherichia coli*, and *Salmonella enterica*) bacteria, a yeast (*Candida albicans*), and a fungus (*Aspergillus niger*) strain are presented in Table 4. As can be seen, only a few compounds show antibacterial activity against the

**Table 3** Synthesis of tetrahydropiperidines **4a–w** in the presence of  $\text{TiCl}_4 \cdot 2\text{H}_2\text{O}$  at room temperature.

Entry	R <sup>1</sup>	R <sup>2</sup>	Time (h)	Lit. time (h)	Yield <sup>a</sup> (%)	Lit. yield (%)	Mp (°C)	Lit. mp (°C)	[Ref]
<b>4a</b>	H	H	8	20	84	81	169–171	175–176	[22]
<b>4b</b>	H	4-Cl	3.5	14	89	85	196–198	201–202	[14]
<b>4c</b>	H	4-Br	4	22	91	81	197–198	197–199	[22]
<b>4d</b>	H	3-I	5	20	89	75	170–172	170–172	[17]
<b>4e</b>	H	4-Me	4	24	90	86	197–198	196–198	[17]
<b>4f</b>	H	4-OMe	6	24	91	74	174–176	172–173	[17]
<b>4g</b>	4-Me	H	5	23	87	68	229–231	230–231	[22]
<b>4h</b>	4-F	H	5	20	89	83	205–207	204–208	[22]
<b>4i</b>	3-Me	H	6	23	84	74	153–154	155–157	[22]
<b>4j</b>	3-Me	4-Me	8	–	86	–	181–182	–	
<b>4k</b>	4-NO <sub>2</sub>	H	6	18	87	80	249–251	247–250	[22]
<b>4l</b>	4-Me	4-Br	5.5	28	89	88	237–239	234–236	[22]
<b>4m</b>	4-Me	4-Cl	5	14	88	79	217–219	218–220	[14]
<b>4n</b>	4-Me	4-F	7	16	85	80	186–187	183–185	[14]
<b>4o</b>	4-Me	3-I	6	20	89	74	205–207	205–207	[17]
<b>4p</b>	4-Me	4-OMe	4	17	91	65	219–220	221–224	[22]
<b>4q</b>	4-Cl	4-Me	4.5	21	92	70	227–228	227–229	[14]
<b>4r</b>	4-Cl	4-F	4	18	89	84	223–224	219–222	[14]
<b>4s</b>	4-Cl	3-I	5	–	87	–	189–190	–	
<b>4t</b>	3-Cl	4-OMe	4	17	90	73	226–227	167–169	[22]
<b>4u</b>	4-OMe	4-Cl	4.5	21	90	84	183–185	180–181	[22]
<b>4v</b>	4-OMe	4-Br	7	21	88	76	184–186	184–186	[22]
<b>4w</b>	4-NO <sub>2</sub>	3-I	5	14	75	77	139–141	140–142	[14]

<sup>a</sup>Isolated yields.**Scheme 2** A plausible mechanism for the synthesis of piperidines **4a–w**.

mentioned bacteria strains. Compound **4w** with nitro and iodo substituents displays the highest activity, while compounds separately substituted with either a nitro group or an iodine atom are devoid of activity.

## Conclusions

A facile and efficient method for the synthesis of highly substituted piperidines was developed. Some of the

**Table 4** Antibacterial activity of the synthesized piperidine derivatives and reference drugs.

Compound	<i>S. enterica</i>		<i>E. coli</i>	
	DD <sup>a</sup>	MIC <sup>b</sup>	DD	MIC
<b>4q</b>	11	750	–	–
<b>4s</b>	10	>1000	–	–
<b>4t</b>	9	NA	–	–
<b>4w</b>	12	750	13	500
Streptomycin (standard)	10	125	15	100
Rifampicin (standard)	10	150	12	125

Compounds with no sensitivity are not reported.

<sup>a</sup>Diffusion diameter (mm).

<sup>b</sup>Minimum inhibitory concentration (μg/mL).

synthesized products exhibit noticeable antibacterial activity.

## Experimental

All reagents were purchased from Merck and Aldrich and used without further purification. Melting points were recorded on an Electro-thermal type 9300 apparatus. FT-IR spectra were recorded using KBr disks on an Avatar 370 FT-IR Thermo Nicolet spectrometer. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were collected on a Bruker Avance 400 spectrometer. Mass spectra were obtained on a Varian Mat CH-7 spectrometer. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyzer.

### General procedure for the preparation of piperidines

#### 4a–w

A solution of aniline or substituted aniline (2 mmol), ethyl acetate (1 mmol), TiCl<sub>4</sub>·2H<sub>2</sub>O (15 mol%) in 96% EtOH (5 mL) was stirred at room temperature. After 20 min, benzaldehyde or substituted benzaldehyde (2 mmol) was added and the mixture was stirred for the time indicated in Table 3. After the completion of the reaction as monitored by TLC using CHCl<sub>3</sub>/MeOH (9:1) as eluent, the resulting solid was filtered off, washed with EtOH (2×20 mL) and crystallized from EtOH. The crude product found in the mother liquor was further purified by column chromatography using CHCl<sub>3</sub>/MeOH (20:1) as eluent and then crystallized from EtOH. Products prepared previously are listed in Table 3.

**Ethyl 2,6-di-m-tolyl-1-(p-tolyl)-4-(p-tolylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4j)** White solid; mp 181–182°C; IR (KBr): 3249, 3068, 2956, 2869, 1649, 1585, 1452, 1372, 1249, 1075 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.46 (3H, t, *J* = 7.2 Hz, CH<sub>3</sub>), 2.17 (3H, s, CH<sub>3</sub>, at phenyl), 2.27 (3H, s, CH<sub>3</sub>, at phenyl), 2.32 (6H, m, CH<sub>3</sub>, at phenyl), 2.70 (1H, dd, *J* = 15.2, 2.2 Hz, C<sub>5</sub>-H'), 2.83 (1H, dd, *J* = 15.2, 5.4 Hz, C<sub>5</sub>-H''), 4.33 (1H, m, OCH<sub>2</sub>), 4.47 (1H, m, OCH<sub>2</sub>), 5.08 (1H, m, C<sub>6</sub>-H), 6.15 (2H, m, ArH), 6.37 (1H, s, C<sub>2</sub>-H), 6.45 (2H, m, ArH), 6.89 (3H, d, *J* = 10.5 Hz), 6.95 (2H, d, *J* = 7.6 Hz), 7.03–7.26 (7H, m, ArH), 10.19 (1H, s,

NH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 14.4, 20.5, 21.2, 21.7, 34.4, 56.2, 58.2, 60.1, 95.1, 113.5, 125.2, 125.5, 127.3, 127.6, 127.8, 128.7, 126.5, 127.2, 128.8, 129.3, 130.1, 135.2, 138.9, 139.4, 146.3, 154.4, 169.6; MS (EI, 70 eV): *m/z* 530 [M<sup>+</sup>]. Anal. Calcd for C<sub>36</sub>H<sub>38</sub>N<sub>2</sub>O<sub>2</sub>: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.40; H, 7.43; N, 5.34.

**Ethyl 2,6-bis(4-chlorophenyl)-1-(3-iodophenyl)-4-((3-iodophenyl)amino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4s)** White solid; mp 189–190°C; IR (KBr): 3234, 3069, 2956, 2875, 1657, 1604, 1459, 1375, 1249, 1075 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.47 (3H, t, *J* = 7.5 Hz, CH<sub>3</sub>), 2.69 (1H, dd, *J* = 14.6, 2.7 Hz, C<sub>5</sub>-H'), 2.82 (1H, dd, *J* = 14.6, 5.4 Hz, C<sub>5</sub>-H''), 4.35 (1H, m, OCH<sub>2</sub>), 4.47 (1H, m, OCH<sub>2</sub>), 5.06 (1H, m, C<sub>6</sub>-H), 6.26 (1H, s, C<sub>2</sub>-H), 6.37–6.46 (4H, m, ArH), 6.55 (1H, s, ArH), 6.74 (2H, d, *J* = 7.6 Hz, ArH), 6.93–7.24 (9H, m, ArH), 10.29 (1H, s, NH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 16.4, 33.9, 55.4, 59.1, 61.9, 99.2, 113.4, 117.4, 121.7, 123.8, 124.2, 125.4, 128.4, 128.8, 129.2, 129.6, 129.9, 130.2, 131.4, 131.7, 133.9, 134.7, 141.4, 142.5, 142.8, 147.9, 155.8, 168.9; MS (EI, 70 eV): *m/z* 793 [M<sup>+</sup>]. Anal. Calcd for C<sub>32</sub>H<sub>26</sub>Cl<sub>2</sub>I<sub>2</sub>N<sub>2</sub>O<sub>2</sub>: C, 48.33; H, 3.30; N, 3.52. Found: C, 48.39; H, 3.21; N, 3.69.

## Antimicrobial activity assays

Antimicrobial activity was determined against three Gram-positive bacteria (*S. epidermidis* ATCC 12228, *S. aureus* ATCC 29737, and *B. subtilis* ATCC 6633) and three Gram-negative bacteria (*S. enteriae* PTCC 1188, *E. coli* ATCC 10536, and *K. pneumonia* ATCC 10031), an yeast (*C. albicans* ATCC 10231), and a fungus (*A. niger* ATCC 16404). Antimicrobial activities of the samples were determined by disc diffusion method through determination of a diameter of inhibition zones [28]. Bacterial strains which were sensitive to the samples in the disc diffusion assay were chosen to study minimal inhibition concentration (MIC) using a micro-well dilution assay method [29]. Streptomycin and rifampicin for bacteria and nystatin for yeast were used as standard reference drugs under concentration conditions identical to that of test compounds.

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