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ANTIMONY TRICHLORIDE AS A MILD AND ACCESSIBLE CATALYST FOR THE ONE-POT SYNTHESIS OF TETRAHYDROPYRIDINES AT ROOM TEMPERATURE

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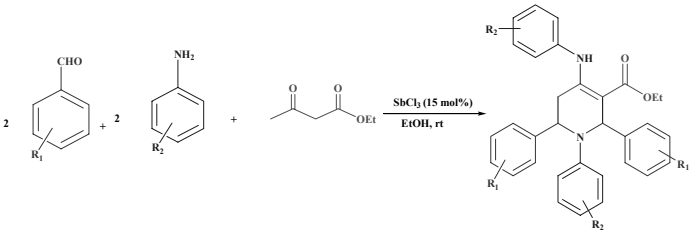
Since tetrahydropyridine and its derivatives as heterocyclic compounds have many biological and pharmaceutical applications in industries, finding an acceptable synthesis yield by an appropriate catalyst is essential. In this study, the synthesis of tetrahydropyridines has been investigated *via* the one pot multicomponent condensation reaction of arylaldehydes, aromatic amines and ethylacetoacetate using $SbCl_3$ as catalyst in ethanol at the room temperature. Some important features of this protocol are: mild reaction conditions, cheap catalyst, convenient workup procedures, unnecessary column chromatography, short reaction times, and high yield of products.



INTRODUCTION

Multicomponent reactions (MCRs) as powerful and effective tools define how three or more different reactants efficiently synthesize complex molecules in one-pot reaction by increasing safety and high atom economy.[1] Additionally, these methods offer rapid and convergent construction of complex molecules without isolation and purification of intermediates, which results in very low waste, time, and cost.[2,3]

Heterocyclic compounds are important structural units of various biological and pharmaceutical products. Among a large variety of nitrogen-containing heterocyclic compounds, tetrahydropyridines and their derivatives are an important class of natural products.[4-5] Tetrahydropyridine applications are very well-known in various biological and pharmaceutical activities such as antihypertensive,[6] anti-bacterial,[7] anti-convulsant, anti-inflammatory[8] and antimalarial.[9] Therefore, synthesis of tetrahydropyridines has been documented with various catalysts such as tetrabutylammonium tribromide (TBATB),[5] L-proline/TFA,[9] $InCl_3$,[10] acetic acid,[11] 1-Methyl-2-oxopyrrolidinium hydrogen sulfate ([Hpyro][HSO_4]),[12] L-proline nitrate,[13] $Bi(NO_3)_3.5H_2O$,[14] citric acid,[15] cerium ammonium nitrate (CAN),[16] $ZrOCl_2.8H_2O$[17] and $Mg(HSO_4)_2$[18]. Some of these procedures are invariably associated with one or more disadvantages such as use of expensive and excess amounts of catalysts, low yields, long reaction times, harsh reaction conditions and tedious workup. Therefore, the development of new methods for the synthesis of tetrahydropyridines is necessary due to their pharmaceutical activities and biological potential during the past years.

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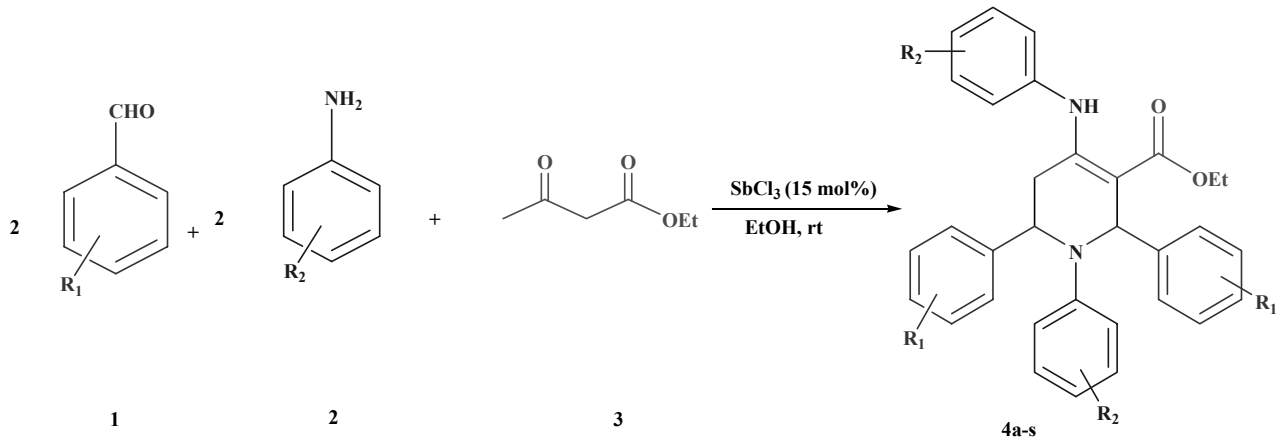
Antimony trichloride has attracted attentions as an inexpensive, commercially available, more convenient than other metal halides, and efficient Lewis acid catalyst in various organic reactions.[19-20]

In continuation of our previous studies on the development of new synthetic methodologies for the production of various heterocycles using MCRs,[21-22] we introduce a simple and efficient procedure for the synthesis of tetrahydropyridines via the condensation of aromatic aldehydes, anilines and ethyl acetoacetate in the presence of $SbCl_3$ as a catalyst (Scheme1).

RESULTS AND DISCUSSION

In a preliminary study, to find the best reaction conditions for the synthesis of tetrahydropyridines, reaction of 4-chloroaniline (2 mmol), ethyl acetoacetate (1 mmol) and benzaldehyde (2 mmol) in ethanol (4 mL) at room temperature is chosen as a reaction model and the results are listed in Table 1.

Initially, the reaction model has been carried out in the absence of the $SbCl_3$ catalyst. As shown in Table 1, entry 1, the reaction was not successful even after prolonged reaction time. In order to use the optimum amount of the catalyst for all reactions, the model reaction was tested using different amounts of SbCl3 catalyst (Table 1, entries 2-5). As demonstrated in Table 1, the best result is obtained in the presence of 15 mol % of the $SbCl_3$ in ethanol at room temperature (Table 1, entry 4). Moreover, increasing the amount of the catalyst does not improve the yield of the product (Table 1, entry 5). Also, the replacement of ethanol with the other solvents such as MeOH, MeCN, EtOAc, THF, H_2O and CH_2Cl_2 decreases the production yield (Table 1, entries 6 −11). In the solvent-free conditions, the product is obtained in moderate yield (47%), which might be due to the fact that reactants have not interacted with the catalyst in the absence of solvent (Table 1, entry 12).



Scheme 1 – Synthesis of tetrahydropyridines in the presence of $SbCl_3$ as catalyst.

Table 1

Optimization of the reaction conditions for the synthesis of **4a**

Entry	Solvent /Condition	Catalyst $SbCl_3$ (mol%)	Time (h)	Yield (%)
1	EtOH/ r.t.	-	20	-
2	EtOH/ r.t.	5	12	50
3	EtOH/ r.t.	10	7	75
4	EtOH r.t.	15	5	92
5	EtOH/ r.t.	20	5	92
6	MeOH/ r.t.	15	5	87
7	MeCN/ r.t.	15	6	78
8	EtOAC/ r.t.	15	16	25
9	THF/ r.t.	15	16	38
10	H_2O/ r.t.	15	16	-
11	CH_2Cl_2/ r.t.	15	16	Trace
12	Neat/ r.t.	15	5	47

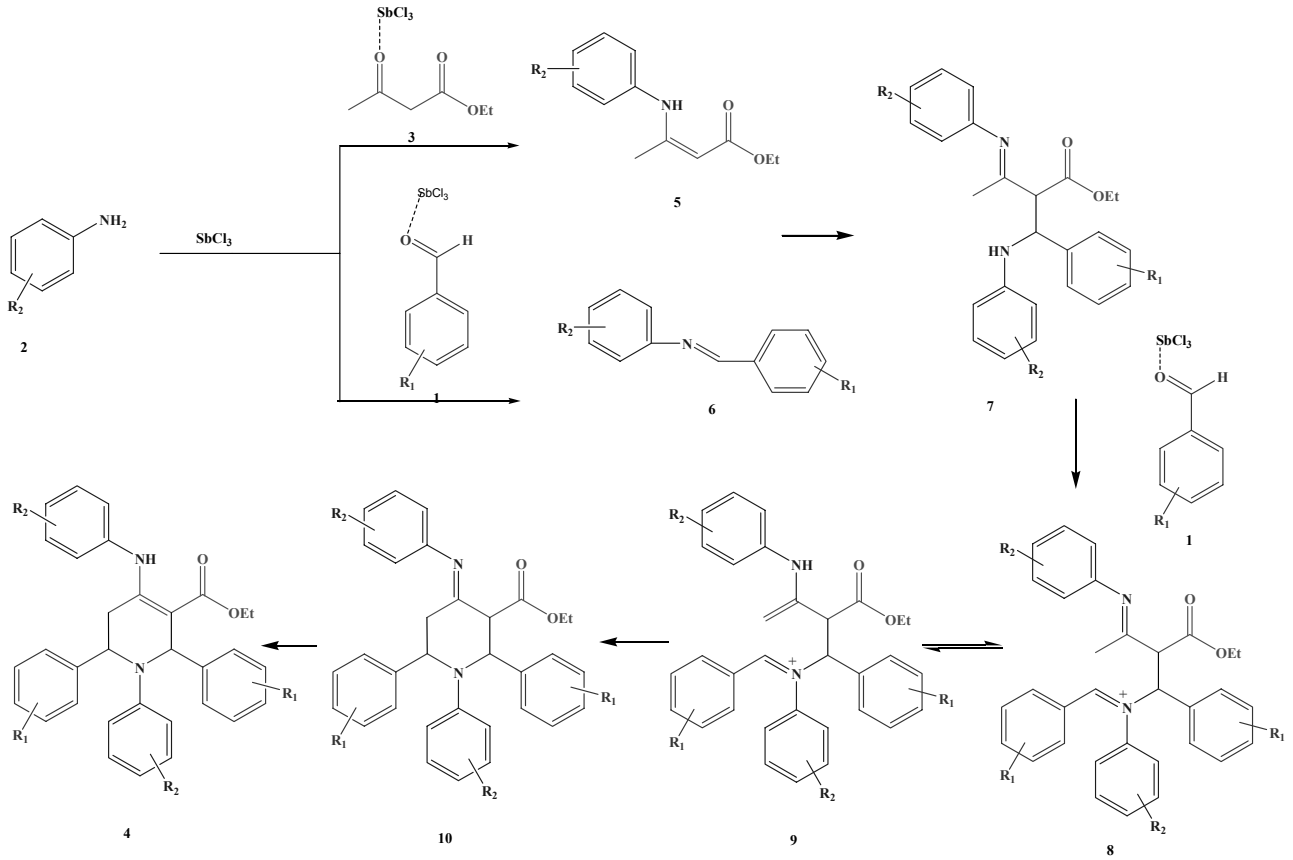
Experimental conditions: benzaldehyde (2 mmol), 4-chloroaniline (2 mmol), ethyl acetoacetate (1 mmol), and solvent (4 mL).

Table 2

One-pot multicomponent synthesis of tetrahydropyridines using $SbCl_3$ as a catalyst

Entry	R1	R2	Product	Time (h)	Yield[a] (%)	M.P. (°C)	
						Found	Lit.[ref.]
1	H	4-Cl	**4a**	5	92	203-204	202-204[15]
2	H	H	**4b**	9	84	171-172	170-171[13]
3	4-Me	4-F	**4c**	6	89	186-187	183-185[12]
4	H	4-Me	**4d**	8	87	199-200	196-198[14]
5	4-OMe	4-Cl	**4e**	4	90	180-182	179-181[13]
6	4-Cl	4-Me	**4f**	5	91	231-232	227-229[14]
7	4-Me	4-OMe	**4g**	8	88	221-222	220-222[14]
8	4-Me	4-Br	**4h**	4	92	233-235	236-238[18]
9	4-OMe	H	**4i**	6	88	164-166	165-167[13]
10	4-NO2	H	**4j**	8	85	247-249	246-248[18]
11	4-Cl	4-OMe	**4k**	5	90	182-184	183-185[18]
12	4-Me	4-Me	**4l**	8	84	166-168	169-171[15]
13	3-Me	H	**4m**	7	84	153-154	155-157[11]
14	4-Me	H	**4n**	7	86	228-229	229-231[14]
15	4-Cl	4-F	**4o**	5	88	220-221	219-222[14]
16	4-Cl	3-Br	**4p**	6	90	182-183	183-185[18]
17	4-OMe	4-Br	**4q**	4	91	185-187	184-186[18]
18	H	3-Br	**4r**	8	89	159-160	...
19	3-Me	4-Cl	**4s**	6	90	200-201	…

a: Isolated product yield



Scheme 2 – The proposed mechanism for the synthesis of tetrahydropyridines catalysed by $SbCl_3$.

Table 3

Comparison of the results of the condensation of benzaldehyde, ethyl acetoacetate and 4-chloroaniline

Entry	Catalyst/ Conditions	Catalyst loading (mol%)	Time (h)	Yield (%)
1	L-proline + Trifluoroacetic acid(TFA) /CH_3CN, r.t[9]	20	21	72
2	1-Methyl-2-oxopyrrolidinium hydrogen sulfate [Hpyro][HSO_4])/EtOH, reflux[12]	15	8	80
3	L-proline nitrate/ MeOH, r.t[13]	10	8	90
4	$Bi(NO_3)_3{\cdot}5H_2O$/ EtOH, r.t[14]	10	16	79
5	Citric acid/ MeOH, r.t[15]	20	24	80
6	Cerium Ammonium Nitrate (CAN)/ CH_3CN, r.t[16]	15	35	68
7	$Mg(HSO_4)_2$/ CH_3CN, r.t[18]	25	24	72
8	$SbCl_3$/ EtOH, r.t	15	5	92

To screen the efficiency of $SbCl_3$ as a catalyst for this multicomponent reaction, different aromatic aldehydes **1** and anilines **2** were treated with ethyl acetoacetate **3** under the optimized reaction condition. The results in Table 2 show that all of the reactions occurred successfully and the corresponding products **4** have been obtained in high yields. However, all aromatic aldehydes/ mine containing electron-withdrawing groups or electron-donating groups were employed and reacted well to afford the corresponding product **4** in good to excellent yields under these reaction conditions

The structures of products were identified by comparing melting points and spectroscopic data with literature reports. The structures of new products **4r** and **4s** were also confirmed by utilizing elemental analysis and spectral data (FT-IR, ^{1}H NMR, ^{13}C NMR, mass spectroscopy).

A plausible mechanism for the formation of tetrahydropyridines is proposed in Scheme 2.[14,16] It is expected that arylamine (2) reacts with ethyl acetoacetate (3) to give enamine (5) in the presence of $SbCl_3$, which also reacts with arylaldehyde (1) to provide imine (6) with elimination of water. The role of $SbCl_3$ as a Lewis acid is to activate the carbonyl group of the aldehyde to promote the reaction. Next, enaminone (5) attacks on the activated imine (6) in the presence of $SbCl_3$ as a Lewis acid via intermolecular Mannich-type reaction to afford the intermediate (7). The intermediate (7) reacts with the second arylaldehyde results another intermediate (8) by the loss of water. Tautomerization stability of intermediate (8) is caused by intramolecular hydrogen bonding. Then, intramolecular Mannich-type reaction forms the intermediate (10). In the final step, tautomerization of the intermediate (10) generates the desired product (4).

The yield and production time of tetra-hydropyridines was compared with other catalyst and methods with respect to the catalyst mole percentage in Table 3. As shown in Table 3, $SbCl_3$ catalyst gives the highest yield with shorter reaction times compared with other catalysts used for tetrahydropyridines production.

EXPERIMENTAL

1. Materials

All reagents were purchased from Merck and Aldrich and used without further purification. Melting points were recorded on an Electrothermal apparatus type 9100 without correction. FT-IR spectra by using KBr pellets were recorded on an Avatar 370 FT-IR Thermo-Nicolet spectrometer. NMR spectra have been collected by Bruker Avance spectrometer type 400 MHz. Mass spectra have been measured by Varian Mat CH-7 at 70 eV. Elemental analysis was done on a Thermo Finnigan Flash EA microanalyzer.

2. General procedure for the synthesis of tetrahydropyridines

A solution of aromatic amine (2.0 mmol) and ethyl acetoacetate (1.0 mmol) in EtOH (4 mL) was stirred for 20 min in the presence of 15 mol% $SbCl_3$ at the room temperature. Then, the aromatic aldehyde (2.0 mmol) was added to the mixture and stirred for the appropriate times as shown in Table 2. The reaction progress was tracked by thin-layer chromatography (TLC). After reactions were completed, the thick precipitate was filtered off and washed away with acetonitrile, and then dried in air subsequently. Spectral results of selected products have been shown below.

2.1. Ethyl-(3-bromophenyl)-4-(3-bromophenylamino)-2,6-bis(phenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate **(4r).**

White solid; m.p: 159-160 °C; IR (KBr): 3244, 3064, 2978, 2834, 1647, 1604, 1462, 1370, 1248, 1068 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50 (3H, t, J = 7.2 Hz, CH_3), 2.71 (1H, dd, J = 15.2, 2.0 Hz, C_5-H′), 2.84 (1H, dd, J = 15.2, 5.4Hz, C_5-H″), 4.35 (1H, dq, J = 10.8, 7.2 Hz, O-CH_2), 4.47 (1H, dq, J = 10.8, 7.0 Hz, O-CH_2), 5.15 (1H, m, C_6-H), 6.27-

6.35 (1H, m, ArH), 6.39 (1H, s, C_2-H), 6.48 (1H, m, ArH), 6.64 (2H, t, J = 7.0 Hz, ArH), 6.74 (1H, t, J = 7.2 Hz, ArH), 6.85 (2H, d, J = 7.2 Hz, ArH), 6.94 (1H, d, J = 6.0 Hz, ArH), 7.12-7.27 (9H, m, ArH), 7.35 (1H, d, J = 6.8 Hz, ArH), 10.29 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.7, 34.8, 56.1, 59.5, 61.4, 94.8, 96.3, 99.6, 113.3, 122.5, 126.2, 126.4, 126.9, 127.1, 127.3, 127.5, 128.1, 129.2, 130.4, 132.3, 135.2, 136.7, 141.3, 141.9, 144.7, 148.9, 155.3, 169.4; MS (m/z): 632; Elemental analysis for: $C_{32}H_{28}Br_2N_2O_2$: C, 60.78; H, 4.46; N, 4.43. Found: C, 60.63; H, 4.38; N, 4.49%.

***2.2 Ethyl-(4-chlorophenyl)-4-(4-chlorophenylamino)-2,6-bis(3-tolyl)-1,2,5,6-tetrahydropyridine-3-carboxylate* (4s).**

White solid; m.p: 200-201 °C; IR (KBr): 3242, 3074, 2969, 2864, 1644, 1608, 1449, 1375, 1258, 1072 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 1.49 (3H, t, J = 7.6 Hz, CH_3), 2.34 (3H, s, Ar-CH_3), 2.38 (3H, s, Ar-CH_3), 2.65 (1H, dd, J = 15.2, 2.4 Hz, C_5-H′), 2.83 (1H, dd, J = 15.2, 5.8 Hz, C_5-H″), 4.36 (1H, m, O-CH_2), 4.48 (1H, m, O-CH_2), 5.07 (1H, d, J = 3.6, C_6-H), 6.25-6.29 (2H, m, ArH), 6.43 (1H, s, C_2-H), 6.44–6.48 (2H, m, ArH), 6.75-6.93 (4H, m, ArH), 7.03-7.35 (8H, m, ArH), 10.25 (1H, s, NH); Elemental analysis for: $C_{34}H_{32}Cl_2N_2O_2$: C, 71.45; H, 5.64; N, 4.90; Found: C, 71.39; H, 5.72; N, 4.83%.

CONCLUSION

We have proposed an efficient protocol for the synthesis of tetrahydropyridines through a multicomponent reaction of aromatic amines, aromatic aldehydes and ethyl acetoacetate using $SbCl_3$ as a catalyst in ethanol at room temperature. Some significant advantages of this work are simplicity of reaction, excellent yields and environmentally benign reaction conditions. In addition, this method avoids the use of expensive catalysts, toxic solvents and chromatographic separation.

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