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One-Pot Synthesis of Hantzsch Dihydropyridine Catalyzed by Ionic Liquid (BmimOAc) and the Oxidative Aromatization of Dihydropyridine Using $FeCl_3 \cdot 6H_2O$

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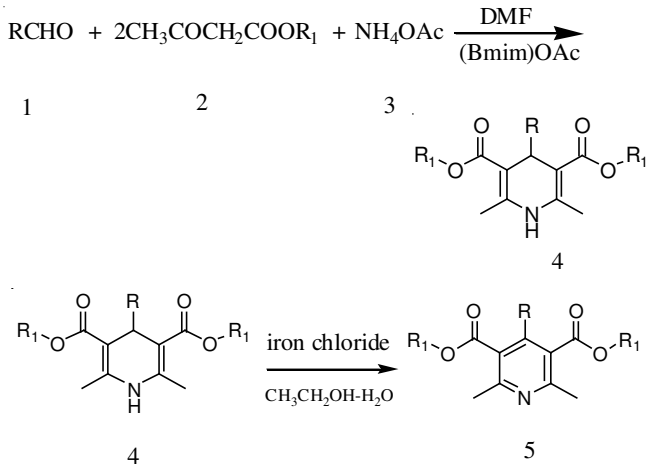
A series of 1,4-dihydropyridines were synthesized in one pot synthesis with the yield of 80-93 % using ionic liquid [bmim]OAc as catalyst and DMF as solvent. The ionic liquid could be repeatedly utilized 5 times with no decrease of the yield. The aromatization of these dihydropyridines (**4a**, **4b**, **4d**, **4f**, **4h** and **4i**) were executed by the action of iron chloride and the post-processing was simplified using ethanol instead of water in dissolving dihydropyridines.

Key Words: Ionic liquid, One pot synthesis, Dihydropyridines, Aromatization.

INTRODUCTION

1,4-Dihydropyridines are a class of model compounds of NADH coenzyme and calcium channel antagonists[1,2]. Because of their promising depressor effect and relatively good tolerability, these compounds have been established as one of the first line drugs for treatment of hypertension. They could be synthesized through the traditional Hantzsch[3] reaction which was put aromatic aldehyde, dicarbonyl compounds and ammonium acetate refluxed for 8-20 h in organic solvent. In the human body, these compounds are oxidized to related pyridine derivatives by the action of cytochrome P-450 in the liver[4], therefore, oxidative aromatization of dihydropyridines has attracted continuing interests of organic and medicinal chemists. Some oxidant such as HNO_3[5], $KMnO_4$[6], SeO_2[7], HIO_3[8], $Mn(OAc)_3$[9], $H_2O_2/Co(OAc)_3$[10], [Mn(III)-BSMP][11], $K_2S_2O_8$[12], I_2[13], *t*-butylhydroperoxide[14] have been reported. However, most of these methods required an extended period of times for completion, utilized large excess of strong or toxic oxidants and produced modest yields of related pyridine.

In present method, the ionic liquid [bmim]OAc was employed as catalyst in the synthesis of dihydropyridine due to its low-toxic, stability, circulation characters, dihydropyridines could be generated with good yield and the use of DMF instead of traditional solvent such as ethanol could shorten the reaction time too. The usage of iron chloride had some advantages such as no by-product appeared due to its moderate oxidability and material was easy to get. Base on this, oxidability of iron chloride was studied. In the aromatization (**Scheme-I**), correspondingly pyridine derivatives were got with good yield in the presence of iron chloride as an oxidant, furthermore. In present works, ethanol instead of H_2O used as solvent for dissolving dihydropyridines, the post-processing for aromatization has been greatly simplified.



Scheme-I: Synthesis and aromatization of dihydropyridine

EXPERIMENTAL

All of the reagents were AR grade, ^{1}H NMR were recorded on a Bruker 400 for $CDCl_3$ solutions and shifts are given in parts per million downfield from TMS as an internal standard. X4-digital melting point reader was used to determine the melting points. Digital thermostat water bath pot was used as heating source; DS-101 magnetic stirrer was used to stir the solutions.

Synthesis of ionic liquid [Bmim]OAc: Sodium acetate (0.82 g, 0.01 mol) dissolved in 30 mL methanol was pour into a 100 mL flask containing [Bmim]Br (2.2 g, 0.01 mol), stirring for 24 h at 30 ºC, the solvent was removed by distillation, the product was added to 15 mL dichloromethane, then white solid NaBr appeared in the bottom of flask, filtrated under vacuum. Solvent dichloromethane was removed by distillation; mother liquid was dried to constant weight at 70 ºC under vacuum, 1.32 g yellow liquid was obtained (yield 90.5 %).

Synthesis of dihydropyridine (4a-k): To a flask containing 20 mL DMF, benzaldehyde (1 mL, 0.01 mol), dicarbonyl compounds (1.75 mL, 0.02 mol), ammonium acetate (1.52 g, 0.02 mol) and [Bmim]OAc (0.16 g, 1 mmol) was added. The mixture was stirred at reflux temperature for 4.5 h. DMF was removed under reduced pressure, yellow solid appeared, washed with 10 mL H_2O, filtrated under reduced pressure, the crude product was recrystallized from 95 % ethanol to give **4a** (2.7 g, 82.3 %). The water layer extracted by 10 mL ether, the ether was removed, dried under vacuum, ionic liquid could be prepared for use next time after. Compounds **4a-k** (Table-1) were prepared with the yield of 81.0-92.2 % (Table-2) using the same procedure as **4a**.

TABLE-1
COMPOUND **4a-k**

Entry	Product	R	R_1
1	**4a**	C_6H_5	Et
2	**4b**	*o*-$NO_2C_6H_4$	Et
3	**4c**	*m*-$NO_2C_6H_4$	Me
4	**4d**	*m*-$NO_2C_6H_4$	Et
5	**4e**	*p*-$CH_3OC_6H_4$	Me
6	**4f**	*p*-$CH_3OC_6H_4$	Et
7	**4g**	CH_3	Et
8	**4h**	CH_3	Me
9	**4i**	H	Et
10	**4j**	H	Me
11	**4k**	C_4H_3O	Et

Diethyl 1,4-dihydro-2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate (4a): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.27 (t, 6H, 2 × CH_3, *J* = 6. 8 Hz), 2.31 (s, 6H, 2 × CH_3), 4.21 (q, 4H, 2 × CH_2O, *J* = 7.7 Hz), 5.03 (s, 1H, CH), 5.60 (s, 1H, NH), 7.30-7.49 (m, 5H, Arh); IR (KBr, ν_{max}, cm^{-1}): 3374, 3010, 1709, 1690, 1500,1330, 1300, 1200, 1115, 1070, 1010, 726.

Diethyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-pyridine-3,5-dicarboxylate (4b): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.29 (t, 6H, 2 × CH_3, *J* = 6.8 Hz),2.37(s, 6H, 2 × CH_3), 4.33 (q, 4H, 2 × CH_2O, *J* = 7.5 Hz), 5.21 (s, 1H, CH), 7.30-7.58 (m, 4H, ArH), 8.77 (s, 1H, NH); IR (KBr, ν_{max}, cm^{-1}): 3410, 3009, 1724, 1707, 1342, 1215, 1109, 844.

Dimethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine-3,5-dicarboxylate (4c): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.35 (s, 6H, 2 × CH_3), 3.75 (s, 6H, 2 × CH_3O), 4.99 (s, 1H, CH), 7.38-7.84 (m, 4H, ArH), 8.89 (s, 1H, NH); IR (KBr, ν_{max}, cm^{-1}): 3321, 3058, 1669, 1660, 1475, 1366, 1226, 1021, 702.

Diethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine-3,5-dicarboxylate (4d): ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.39 (t, 6H, 2 × CH_3, *J* = 6.8 Hz), 2.41 (s, 6H, 2 × CH_3), 4.45 (q, 6H, 2 × CH_2O, *J* = 7.5 Hz), 4.99 (s, 1H, CH), 7.58-7.94 (m, 4H, ArH), 8.91 (s, 1H, NH); IR (KBr, ν_{max}, cm^{-1}): 3343, 3095, 2985, 1705, 1647, 1487, 1212, 1021, 787, 742.

Dimethyl 1,4-dihydro-4-(4-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (4e): ^{1}H NMR (400 MHz, $CDCl_3$), δ: 2.26 (s, 6H, 2 × CH_3), 3.55 (s, 6H, 2 × CH_3O), 3.87 (s, 3H, CH_3O), 5.01 (s, 1H, CH), 7.38-7.64 (m, 4H, ArH), 8.49 (S, 1H, NH); IR (KBr, ν_{max}, cm^{-1}): 3401, 3158, 1677, 1658, 1395, 1366, 1226, 1007, 693.

Diethyl 1,4-dihydro-4-(4-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (4f): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.13 (t, 6H, 2 × CH_3, *J* = 6.8 Hz), 2.35 (s, 6H, 2 × CH_3), 3.84 (s, 3H, CH_3O), 4.10 (q, 4H, 2 × CH_2O, *J* = 7.5 Hz,), 5.07 (s, 1H, CH), 7.20-8.00 (M, 4H, ArH); 8.94 (S, 1H, NH); IR (KBr, ν_{max}, cm^{-1}): 3370, 3004, 1719,1677,1479, 1411, 1346, 1210, 693.

Diethyl 1,4-dihydro-2,4,6-trimethylpyridine-3,5-dicarboxylate (4g): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.19 (d, 3H, *J* = 6.4 Hz), 1.29 (t, 6H, 2 × CH_2CH_3, *J* = 6.8 Hz), 2.32 (s, 6H, 2 × CH_3), 3.85 (q, 1H, CH, *J* = 6.0 Hz), 4.20 (q, 6H, 2 × CH_2O, *J* = 7.2 Hz), 5.56 (s, 1H, NH); IR (KBr, ν_{max}, cm^{-1}): 3346, 3010, 1707, 1687, 1421, 1241, 1009.

Dimethyl 1,4-dihydro-2,4,6-trimethylpyridine-3,5-dicarboxylate (4h): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.17 (d, 3H, *J* = 6.4 Hz), 2.27 (s, 6H, 2 × CH_3), 3.45 (s, 6H, 2 × OCH_3) 3.85 (q, 1H, CH, *J* = 6.0 Hz), 5.56 (s, 1H, NH); IR (KBr, ν_{max}, cm^{-1}): 3319, 3000, 1702, 1664, 1361, 1208, 1029.

Diethyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (4i): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.29 (t, 6H, 2 × CH_2CH_3, *J* = 6.8 Hz), 2.32 (s, 6H, 2 × CH_3), 3.28 (s, 2H, CH_2), 4.10 (q, 4H, 2 × CH_2O, *J* = 6.8 Hz), 5.48 (s, 1H, NH); IR (KBr, ν_{max}, cm^{-1}): 3346, 3010, 1707, 1687, 1421, 1241, 1009.

TABLE-2
PHYSICAL DATA OF COMPOUND **4a-k**

Compound	Product	Time (h)	m.p. (ºC) (found/lit.)	Yield (%) (found/lit.)
4a	Yellow solid	4.50	156-158/157-159[15]	82.3/74.0[17]
4b	Yellow solid	4.00	125-127/123-124[16]	87.7/74.3[16]
4c	White crystal	1.50	207-210/210-212[17]	91.4/75.0[17]
4d	Yellow crystal	2.50	168-170/162-164[18]	85.0/84.2[16]
4e	Yellow solid	3.00	193-194	92.2
4f	Yellow solid	3.00	161-163/158-159[16]	88.0/75.6[16]
4g	Yellow solid	2.50	126-130	86.3
4h	Yellow solid	0.75	154-157	82.5
4i	Yellow solid	2.00	182-184/183-185[18]	90.7/86.3[16]
4j	Yellow solid	1.50	231-234	81.0
4k	Yellow solid	1.00	160-162/161-162[19]	87.3/88.3[19]

Dimethyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (4j): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.32 (s, 6H, 2 × CH_3), 3.28 (s, 2H, CH_2), 3.86 (s, 3H, CH_3O), 5.53 (s, 1H, NH); IR (KBr, ν_{max}, cm^{-1}): 3246, 3100, 1698, 1666, 1401, 1241, 909.

Diethyl 4-(furan-yl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (4k): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30 (t, 6H, 2 × CH_2CH_3, *J* = 6.7 Hz), 2.33 (s, 6H, 2 × CH_3), 4.18 (q, 4H, 2 × OCH_2, *J* = 6.8 Hz), 5.47 (s, 1H, NH), 5.75 (s, 1H, CH), 5.96 (d, 1H, CH=, *J* = 2.8 Hz), 6.23 (t, 1H, CH=, *J* = 3.2 Hz), 7.23 (d, 1H, C=, *J* = 4.2 Hz); IR(KBr, ν_{max}, cm^{-1}): 3327, 3149, 1698, 1684, 1657, 1329, 1047.

Synthesis of 5 (the aromatization of dihydropyridine): 5 mmol compound **4** was dissolved in 20 mL of ethanol and poured into a flask containing iron chloride ($FeCl_3 \cdot 6H_2O$) (4.05 g, 15 mmol) dissolved in 10 mL H_2O, 3 drops of acetic acid were added dropwise, stirring at 80 ºC, monitored by TLC. Once the reaction completed, the solvent was removed by distillation, crude product was washed to neutrality by 20 mL H_2O. The phases were separated and the aqueous phase was additionally extracted with dichloromethane (10 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to dryness. The crude products were purified by passing through column of silica gel eluted with mixture of petroleum ether and dichloromethane (v/v, 1:2) to give compound 5 (purity > 99 %) as shown in Table-3.

TABLE-3
DATA OF OXIDATIVE AROMATIZATION OF DIHYDROPYRIDINES IN THE PRESENCE OF IRON CHLORIDE AS AN OXIDANT

Compound	Time (min)	m.p. (ºC) (found/lit.)	Yield (%)
5a	140	61-64/61-63[11]	94.5
5b	180	71-75/74-76[16]	92.1
5d	120	60-62/62-63[20]	93.7
5f	90	48-50/49-52[11]	90.6
5h	95	Oil	88.7
5i	70	66-67/69-70[18]	75.4

RESULTS AND DISCUSSION

Synthesis of dihydropyridine (4a-k): Ionic liquid has its low-toxic, stable, circulation usage characters, the alkaline [Bmim]OAc could catalyze the Michael-addition in Hantzsch reaction procedure and instead of ethanol, the DMF was employed to act solvent. As the result of the activity of the ionic liquid [Bmim]OAc was much better in aprotic solvent, so the reaction time could be shorten to less than 5 h (Table-2) and the yield were higher than that reported in literature[15-19].

Synthesis of 5 (the aromatization of dihydropyridine): As a calcium channel antagonists, dihydropyridine must be oxidized to pyridine derivatives by the action of cytochrome P-450 in the liver before drainage out of the body. Therefore, oxidative aromatization of dihydropyridines has attracted continuing interests of organic and medicinal chemists. Some oxidants, such as HNO_3, $KMnO_4$ and H_2O_2 have been reported. However, the utilization of these oxidant are either highly toxic and expensive or generate some by-products which are difficult to be removed or present serious disposal problems. Iron chloride as a low-toxic oxidant was used in aqueous medium have been reported. The aromatization was carried out in aqueous (with some drop of acetic acid in it) with the iron chloride as oxidant, then adjust the pH to neutral through sodium carbonate solution. But it is found in present work that compound **4** was difficult to dissolve in water which hindered the reaction, extended the reaction time and decreased the yield. Further more, in post-processing, sodium carbonate solution was added to adjust the pH to neutral, but with the drop of the sodium carbonate solution, some unnecessary product such as iron(II) or iron(III) precipitation appeared that led to the separation and purification of the product more difficult. In this work, compound **4** was dissolved in ethanol and iron chloride dispersed in H_2O, after the reaction was over, solvent was removed under reduced pressure. The crude product deposited, washed with water instead of adding alkali to make the solution to a neutral, aqueous was extracted by dichloromethane combined with the organic layers and removed solvent to afford **5** with good yield. Formation of **5** was characterized by the IR and ^{1}H NMR spectra. For compound **5d**, the disappearance of signals of C-H at 4.99 ppm and N-H at 8.91 ppm in ^{1}H NMR and the appearance of band at 1606 cm^{-1} in the IR data which attribute to the pyridine skeleton were found which showed the oxidative aromatization was generated. Characterizations of the other compounds (**5a**, **5b**, **5f**, **5h** and **5i**) from IR and ^{1}H NMR spectra were similar to **5d** (Table-4).

TABLE-4
^{1}H NMR AND IR SPECTRA OF COMPOUND **5a-k**

Compound	^{1}H NMR (400 MHz, $CDCl_3$) δ/IR (KBr, ν_{max}, cm^{-1})
5a	1.31 (t, 6H, 2 × CH_3, *J* = 6. 8 Hz), 2.59 (s, 6H, 2 × CH_3), 4.33 (q, 4H, 2 × CH_2O, *J* = 7.6 Hz), 7.51-7.87 (m, 5H, ArH)/2985, 1725, 1607, 1500, 1330, 1300, 1200, 1115, 1070, 1021, 747.
5b	1.33 (t, 6H, 2 × CH_3, *J* = 6. 8 Hz), 2.67 (s, 6H, 2 × CH_3), 4.51 (q, 4H, 2 × CH_2O, *J* = 7.5 Hz), 7.55-7.92 (m, 4H, ArH)/2982, 1728, 1578, 1448, 1285, 1232, 1108, 1041, 817, 778.
5d	1.39 (t, 6H, 2 × CH_3, *J* = 6.8 Hz), 2.62 (s, 6H, 2 × CH_3), 4.63 (q, 6H, 2 × CH_2O, *J* = 7.2 Hz), 7.59-7.94 (m, 4H, ArH)/3095, 2985, 1705, 1647, 1606, 1487, 1258,1066, 810, 776.
5f	1.09 (t, 6H, 2 × CH_3, *J* = 6.4 Hz), 2.53 (s, 6H, 2 × CH_3), 3.84 (s, 3H, CH_3O), 4.11 (q, 4H, 2 × CH_2O, *J* = 7.5 Hz), 7.50-8.17 (m, 4H, ArH)/3004, 2927, 1716, 1693, 1597, 1503, 1300, 1142, 969, 833, 767.
5h	1.97 (s, 3H, CH_3), 2.57 (s, 6H, 2 × CH_3), 3.88 (s, 6H, 2 × CH_3O)/3039, 3000, 1709, 1698, 1642, 1599, 1521, 1227, 1001.
5i	1.38 (t, 6H, 2 × CH_2CH_3, *J* = 6.8 Hz), 2.62 (s, 6H, 2 × CH_3), 4.78 (q, 4H, 2 × OCH_2, J = 7.4 Hz), 7.85 (s, 1H, C=CH)/3010, 1707, 1687, 1642, 1589, 1241, 1007.

Conclusion

That non-toxic ionic liquid (BmimOAc) was employed as catalyst, DMF as solvent not only raise the solubility of dihydropyridine but also enhance the activity of catalyst. The dihydropyridine could be acquired with good yield in short time and the catalyst could be repeatedly used 5 times with no decrease of the yield. Pyridine derivatives transformed from dihydropyridine were got with good yield and no by-product been found as the moderate oxidability of iron chloride. Post-

processing of pyridine derivative was conveniently and efficiently improved. All the compounds were confirmed by IR and ^{1}H NMR spectra.

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