Synthesis of Symmetrical 1, 4-Dihydropyridine Derivatives in Ionic Liquid

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Summary: symmetrical 1, 4-dihydropyridine derivatives **4(a-o)** were synthesized in ionic liquid [Bmim]Cl·$AlCl_3$ for 2-4 h with the 70%-90% yield, and the ionic liquid could be utilized for 5 times repeatedly with the no decrease of the yield.

Key words: Symmetrical, Ionic liquid, Knoevenagel, Michael addition reaction, One-pot synthesis.

Introduction

1,4-dihydropyridine derivatives are a class of important heterocyclic compounds, and was used as high-performance calcium antagonists since 1960's. Because of their potential biological activity [1-3] and use in treatment such as anti-hypertensive[4], anti-inflammatory[5] and antiangina[6] drugs, it has been paid more and more attention in recent years.

Traditional Hantzsch reaction [7-9] was put aldehyde, dicarbonyl compounds and ammonium acetate reflux for 8-20 h in organic solvent, which existed time was long, solvent was toxic and high costs disadvantages.

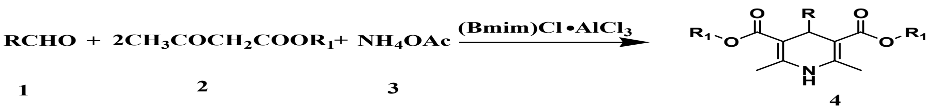
Ionic liquids are environmentally benign alternative solvents for various chemical processes. They have attracted the attention of chemists owing to their unique physical and chemical properties [10-11]. Because of their low vapor pressure, ionic species do not contribute to volatile organic compound emission. They have also been referred to as 'designer solvents'[12] since their properties can be altered by the fine tuning of parameters such as the choice of the organic cation, inorganic anion and alkyl chain attached to the organic cation. These structural variations provide an opportunity to devise the most idealized solvent needed for a particular chemical process. Several reactions have been carried out in ionic liquids [13] including the Biginelli, Diels–Alder, Wittig and Pechman reactions, the benzoin condensation, catalytic hydrogenation and several enzyme catalysed reactions[14].

Chloroaluminate ionic liquids have been used in Friedel–Crafts and other reactions where they play the dual role of both the Lewis acid catalyst and the solvent [13]. Thus, we decided to investigate the Hantzsch synthesis under these conditions. Here we report a new synthesis of DHP in the presence of the Lewis acid [Bmim]Cl•$AlCl_3$ ionic liquid. By the help of ionic liquid, the reaction time could be shortened to 2-4 h with no by-product appeared, and the ionic liquid could be utilized for 5 times repeatedly with no decrease of the yield. It was a green, efficient, simple and novelty.

Results and discussion

Synthesis of 3-ethyl 5-alkyl 2-(chloromethyl)-1, 4-dihydro-6-methyl-4-(substituent phenyl) pyridine-3, 5-dicarboxylate [**4(a-o)**]

Ionic liquid possessing its low-toxic, stable, circulation usage characters, could catalyze the Michael-addition in hantzsch reaction procedure, employed to act both solvent and catalyst in the Hantzsch reaction as the result of the activity of the ionic liquid [Bmim]Cl·$AlCl_3$ was much better than only protic solvent and aprotic solvent, so the reaction time could be shorten to less than 4 h and the yield were higher than that reported in literature[15-20]. The reaction condition was then optimized by conducting the reaction in different temperatures and employing different catalyst loadings. The results are summarized in Table-1. It is evident that the best result was obtained by the application of at 80°C (Table-1, entry 13), the adequate proportion of $AlCl_3$ /[Bmim]Cl is 2:1, Higher proportion of $AlCl_3$ /[Bmim]Cl reduce the amount of yield as side products formed.



Scheme. 1: The preparation of symmetrical 1, 4-dihydropyridine derivatives in ionic liquid

Table-1: Condensation of carboxaldehyde, ethyl acetoacetate and ammonium acetate catalyzed in 10mL [Bmim]Cl•$AlCl_3$ under different proportion, temperature and solvent systems

Entry	$AlCl_3$: [Bmim]Cl	Solvent amount (mL)	Temperature (°C)	Time (h)	Yield (%)
1	1.2	EtOH ^{a},	rt	24	41
2	1.2	EtOH ^{a}	60	1.5	54
3	1.2	EtOH ^{a}	60	3	67
4	1.2	No ^{c}	60	3	66
5	1.2	No ^{c}	80	2	76
6	1.5	No ^{c}	60	1.5	76
7	1.5	No ^{c}	80	1.5	78
8	1.5	EtOH ^{a}	60	3	66
9	1.5	EtOH ^{a}	80	3	77
10	1.5	Dioxane^{a}	60	2.8	57
11	2.0	EtOH ^{a}	60	2.8	84
12	2.0	Dioxane	80	2.8	86
13	2.0	No ^{c}	80	2.8	91
14	2.5	EtOH ^{a}	80	2.8	78
15	2.5	Dioxane^{a}	80	2.8	77
16	2.5	No ^{c}	80	3	84
17	2.0	No ^{d}	80	3	90
18	2.0	No ^{e}	80	3	90

a: 5 mL [Bmim]Cl•$AlCl_3$ and 5mL EtOH; b: 10 mL solvent; c: 10 mL [Bmim]Cl•$AlCl_3$; d: 10 mL ionic liquid which used for 2 times; e: 10 mL ionic liquid which used for 4 times.

The synthesis (scheme. 1) of ***4a-o*** involves a Michael addition and ring-closure reaction, traditional method was reflux in ethanol for 8-20 h, which suffered from drawbacks such as long reaction times, occurrence of several by-products, and the use of large amount of reagents. Therefore, ionic liquid were synthesized and attempted to improve this reaction, by comparison, we found that ionic liquid [Bmim]Cl•$AlCl_3$ was effective to shorten reaction time and improve the yield (Table-2). When the reaction was over, the ionic liquid was extracted with ether(10 mL×3), than the ether removed by distillation, ionic liquid could be utilized for 5 times repeatedly with the no decrease of the catalytic effect (Table-1, entry 17, 18). It is obvious that ionic liquid [Bmim]Cl•$AlCl_3$ was an effective, green and novelty in synthesis of 1, 4-dihydropyridine derivatives.

Experimental

All of the reagents are AR grade. Melting points were determined on an X4-degital melting points reader and uncorrected. ^{1}HNMR spectra were run at a Bruker 400 for $CDCl_3$ solutions and shifts are given in parts per million downfield from TMS as an internal standard. Elemental analyses were performed in a Fash-1112 instrument. The IR spectra were taken on a NEXUS 470 FT-IR spectrometer (KBr disks). Mass spectra were recorded on ESQUIRE 3000 Mass Spectrometer.

The preparation of Ionic Liquid [Bmim]Cl·$AlCl_3$

To a flask containing 50 g [Bmim]Cl which was dried for 5 h at 80 °C under vacuum, a certain amount of anhydrous aluminum chloride was added under nitrogen, stirring until aluminum chloride was completely dissolved and transparent yellowish ionic liquid [Bmim]Cl·$AlCl_3$ ([Bmim]Cl:$AlCl_3$ =1:1-2) afforded, placed in a desiccators.

Table-2: 1,4-Dihydropyridine Derivatives 4.

compound	R	R_1	Time (h)	M.p (°C)(Found/Lit.)	Yield (%) (Found / Lit.)
4a	C_6H_5	Et	4.0	156-158/157-159[15]	82.3/74.0[17]
4b	O-$NO_2C_6H_4$	Et	4.0	125-127/123-124[16]	87.7/74.3[16]
4c	m-$NO_2C_6H_4$	Me	1.5	207-210/210-212[17]	91.4/75.0[17]
4d	m-$NO_2C_6H_4$	Et	2.5	168-170/162-164[18]	85.0/84.2[16]
4e	p-$CH_3OC_6H_4$	Me	3.0	193-194	92.2
4f	p-$CH_3OC_6H_4$	Et	3.0	161-163/158-159[16]	88.0/75.6[16]
4g	CH_3	Et	2.5	126-130	86.3
4h	CH_3	Me	1.7	154-157	82.5
4i	H	Et	2.0	182-184/183-185[18]	90.7/86.3[16]
4j	H	Me	1.5	231-234	81.0
4k	C_4H_3O	Et	1.0	160-162/161-162[19]	87.3/88.3[19]
4l	o-$CH_3C_6H_4$	Me	2.3	160-162/160-163[20]	84.3
4m	m -$CH_3C_6H_4$	Me	2.5	189.5–191.0[20]	88.6
4n	p-$CH_3C_6H_4$	Me	2.0	168.5–171.0[20]	85.6
4o	2,4-$(CH_3)_2C_6H_3$	Me	3.0	191.5–193.5[20]	79.5

General Procedure for the Hantzsch Condensation

The ester derivatives were prepared by the reaction of **1** (0.03 mol), **2** (0.06 mol) and **3** (0.03 mol) stirring for 2-4 h in 10 mL ionic liquid [Bmim]Cl•$AlCl_3$ at 80 ℃, then the organic layer were extracted with ether(10 mL×3), solvent were removed by distillation, **4a-o** (Table-2) were deposited**,** yellow solid appeared, washed with 10 mL H2O, filtrated under reduced pressure, the crude product was recrystallized from 95 % ethanol. 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.

Diethyl 1,4-dihydro-2, 6-dimethyl-4-phenylpyridine-3, 5-dicarboxylate **(4a)**

Yellow crystals; ^{1}HNMR(400MHz, $CDCl_3$) 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); Anal. Calcd for $C_{19}H_{23}NO_4$: C 69.28, H 7.04, N 4.25; found: C 69.25, H 7.01, N 4.20. IR (KBr) ν: 3374, 3010, 1709, 1690, 1500, 1330, 1300, 1200, 1115, 1070, 1010, 726 cm^{-1}.

Diethyl 1,4-dihydro-2, 6-dimethyl-4-(2-nitrophenyl)pyridine-3, 5-dicarboxylate **(4b)**

Yellow crystals; ^{1}HNMR(400MHz, $CDCl_3$) 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); Anal. Calcd for $C_{19}H_{22}N_2O_6$: C 60.95, H 5.92, N 7.48; found: C 60.89, H 5.89, N7.42. IR (KBr) ν:3410, 3009,1724, 1707, 1342, 1215, 1109, 844 cm^{-1}.

Dimethyl 1,4-dihydro-2, 6-dimethyl-4-(3-nitrophenyl)pyridine-3, 5-dicarboxylate **(4c)**

Yellow crystals; ^{1}HNMR (400MHz, $CDCl_3$) 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); Anal. Calcd for $C_{17}H_{21}N_2O_6$: C 58.96, H 5.24, N 8.09; found: C 58.91, H5.22, N8.02. IR (KBr) ν:3321, 3058, 1669, 1660, 1475, 1366, 1226, 1021, 702 cm^{-1}.

Diethyl 1, 4-dihydro-2, 6-dimethyl-4-(3-nitrophenyl)pyridine-3, 5-dicarboxylate **(4d)**

Yellow crystals; ^{1}HNMR(400MHz, $CDCl_3$), δ: 1.39(t, 6H, 2×CH_3, J= 6.8Hz), 2.41 (s, 6H, 2 ×CH_3), 4.45 (q, 6H, 2 ×CH_2O, J=7.5Hz), 4.99 (s, 1H, CH), 7.58-7.94 (m, 4H, ArH), 8.91(s, 1H, NH); Anal. Calcd for $C_{19}H_{22}N_2O_6$: C 60.95, H 5.92, N 7.48; found: C 60.90, H 5.96, N7.40. IR(KBr) ν: 3343, 3095, 2985, 1705, 1647, 1487, 1212, 1021, 787, 742 cm^{-1}.

Dimethyl 1, 4-dihydro-4-(4-methoxyphenyl)-2, 6-dimethylpyridine-3, 5-dicarboxylate **(4e)**

Yellow crystals; ^{1}HNMR (400MHz, $CDCl_3$), 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); Anal. Calcd for $C_{19}H_{21}NO_5$: C 65.24, H 6.39, N 4.23; found: C 65.19, H 6.34, N 4.28. IR (KBr) ν:3401, 3158, 1677, 1658, 1395, 1366, 1226, 1007, 693 cm^{-1}.

Diethyl 1, 4-dihydro-4-(4-methoxyphenyl)-2, 6-dimethylpyridine-3, 5-dicarboxylate **(4f)**

Yellow crystals; ^{1}HNMR (400MHz, $CDCl_3$) 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. 5Hz,), 5.07 (s, 1H, CH), 7.20-8.00 (M, 4H , ArH); 8.94(S, 1H, NH); Anal. Calcd for $C_{21}H_{25}NO_5$: C 66.83, H 7.01, N 3.90; found: C 66.79, H 6.96, N 3.98. IR (KBr) ν: 3370, 3004, 1719,1677,1479, 1411, 1346, 1210, 693 cm^{-1} .

Diethyl 1, 4-dihydro-2, 4, 6-trimethylpyridine-3, 5-dicarboxylate **(4g)**

Yellow crystals; ^{1}HNMR (400MHz, $CDCl_3$) δ: 1.19 (d, 3H, J=6.4Hz), 1.29(t, 6H, 2×CH_2CH_3, J=6.8Hz), 2.32(s, 6H, 2×CH_3), 3.85(q, 1H, CH, J=6.0Hz),4.20(q, 6H, 2×CH_2O, J=7.2Hz), 5.56(s,1H, NH); Anal. Calcd for $C_{14}H_{21}NO_4$: C 62.90, H 7.92, N 5.24; found: C 62.96, H 7.88, N 5.20. IR (KBr) ν:3346, 3010, 1707, 1687, 1421, 1241, 1009 cm^{-1}

Dimethyl 1, 4-dihydro-2, 4, 6-trimethylpyridine-3, 5-dicarboxylate **(4h)**

Yellow crystals; ^{1}HNMR (400MHz, $CDCl_3$) δ: 1.17(d, 3H, J=6.4Hz), 2.27(s, 6H, 2×CH_3), 3.45(s, 6H, 2×OCH_3), 3.85(q, 1H, CH, J=6.0Hz), 5.56(s, 1H, NH); Anal. Calcd for $C_{12}H_{17}NO_4$: C 60.24, H 7.16, N 5.85; found: C 60.20, H 7.13, N5.81. IR(KBr) ν:3319, 3000, 1702, 1664, 1361, 1208, 1029 cm^{-1}.

Diethyl 1, 4-dihydro-2, 6-dimethylpyridine-3, 5-

dicarboxylate **(4i)**

Yellow crystals; ^{1}HNMR (400MHz, $CDCl_3$) δ: 1.29(t, 6H, 2×CH_2CH_3, J=6.8Hz), 2.32(s, 6H, 2×CH_3), 3.28(s, 2H, CH_2), 4.10(q, 4H, 2×CH_2O, J=6.8Hz), 5.48(s, 1H, NH); Anal. Calcd for $C_{19}H_{23}NO_4$: C 69.28, H 7.04, N 4.25; found: C 69.24, H7.00, N4.20. IR(KBr) *v*:3346, 3010, 1707, 1687, 1421, 1009 cm^{-1}.

Dimethyl 1, 4-dihydro-2, 6-dimethylpyridine-3, 5-dicarboxylate **(4j)**

Yellow crystals; ^{1}HNMR (400MHz, $CDCl_3$) 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); Anal. Calcd for $C_{11}H_{15}NO_4$: C 58.66, H 6.71, N 6.22; found: C 58.59, H 6.76, N6.19. IR(KBr) *v*:3246, 3100, 1698, 1666, 1401, 1241, 909 cm^{-1}.

Diethyl 4-(furan-yl)-1, 4-dihydro-2, 6-dimethyl-pyridine-3, 5-dicarboxylate **(4k)**

Yellow crystals; ^{1}HNMR (400MHz, $CDCl_3$) δ: 1.30 (t, 6H,2×CH_2CH_3, J=6.7Hz), 2.33(s, 6H, 2×CH_3), 4.18(q, 4H, 2×OCH_2, J=6.8Hz), 5.47(s, 1H, NH), 5.75(s,1H, CH),5.96(d, 1H, CH=, J=2.8Hz), 6.23(t,1H,CH=, J=3.2Hz), 7.23(d, 1H, C=, J=4.2Hz); Anal. Calcd for $C_{17}H_{21}NO_5$: C 63.94, H6.63, N 4.39; found: C 63.88, H 6.59, N4.36. IR(KBr) *v*:3327, 3149, 1698, 1684,1657, 1329, 1047cm^{-1}.

2,6-Dimethyl-3,5-dimethoxy carbony l-4- (2-methylphenyl)-1,4-dihydropyridine **(4l)**

Yellow crystals; ^{1}H-NMR ($CDCl_3$): δ: 2.30 (s, 6H, Me), 2.54 (s, 2H, Me), 3.61 (s, 6H, OMe), 5.14 (s, 1H, CH), 5.83 (s, 1H, NH), 6.97–7.07 (m, 3H), 7.30 (d, 1H, J=7.4 Hz); Anal. Calcd for $C_{18}H_{21}NO_4$: C 68.55, H 6.71, N 4.44; found: C 68.59, H 6.74, N4.44. IR (KBr): *v*: 3383, 2951, 1690, 1651, 1622, 1337, 1312, 1298, 1252, 1213, 1184, 1145, cm^{-1}.

2,6-Dimethyl-3,5-dimethoxycarbonyl-4-(3-methylphenyl)-1,4-dihydropyridine **(4m)**

Pale yellow crystals; ^{1}H-NMR (CDCl3): δ: 2.27 (s, 3H, Me), 2.29 (s, 6H, Me), 3.64 (s, 6H, OMe), 4.98 (s, 1H, CH), 6.19 (s, 1H, NH), 6.94 (d, 1H, J□7.0 Hz), 7.05–7.12 (m, 3H); Anal. Calcd for $C_{18}H_{21}NO_4$: C 68.55, H 6.71, N 4.44; found: C 68.54, H 6.67, N 4.34. IR (KBr): *v*: 3354, 3247, 1703, 1652, 1626, 1603, 1586, 1489, 1459, 1437, 1266, 1247, 1217, 1187, 1139, 1160, 1123, 1098, 1052, 1017 cm^{-1};

2,6-Dimethyl-3,5-dimethoxycarbonyl-4-(4-methylphenyl)-1,4-dihydropyridine **(4n)**

Yellow crystals; ^{1}H-NMR ($CDCl_3$): δ: 2.27 (s, 3H, Me), 2.30 (s, 6H, Me), 3.64 (s, 6H, OMe), 4.97 (s, 1H, CH), 6.01 (s, 1H, NH), 7.02 (d, 2H, J□7.9 Hz), 7.15 (d, 2H, J□7.9 Hz); Anal. Calcd for $C_{18}H_{21}NO_4$: C 68.55, H 6.71, N 4.44; found: C 68.54, H 6.68, N 4.38. IR (KBr): *v*:□3315, 3250, 3049, 3023, 1698, 1655, 1496, 1381, 1341, 1316, 1305, 1243cm^{-1};

2,6-Dimethyl-3,5-dimethoxycarbonyl-4-(2,4-dimethylphenyl)-1,4-dihydropyridine **(4o)**

^{1}H-NMR ($CDCl_3$): δ: 2.22 (s, 3H, Me), 2.25 (s, 6H, Me), 2.51 (s, 3H, Me), 3.61 (s, 6H, OMe), 5.10 (s, 1H, CH), 6.19 (s, 1H, NH), 6.85 (s, 1H), 6.87 (s, 1H), 7.19 (d, 1H, J□7.7 Hz); Anal. Calcd for $C_{19}H_{23}NO_4$: C 69.28, H 7.04, N 4.25; found: C 69.30, H 7.02, N 4.22. IR(KBr): *v*: 3371, 2990, 1688, 1655, 1148, 1121, 1096, 1051, 1020 cm^{-1}.

Conclusions

Ionic liquid [Bmim]Cl·$AlCl_3$ was prepared, that used as solvent and catalyst in the synthesis of 1,4-dihydropyridine derivatives, It was proved to be effective to shorten reaction time of synthesis of DHP to 2-4 h with yield of 70-90%, and ionic liquid could utilized for 5 times repeatedly with no decrease of the yield.

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