

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

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(Received on 31st August 2010, accepted in revised form 27th July 2012)

Summary: symmetrical 1, 4-dihydropyridine derivatives **4(a-o)** were synthesized in ionic liquid [Bmim]Cl·AlCl₃ 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·AlCl₃ 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·AlCl₃ 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 AlCl₃ / [Bmim]Cl is 2:1, Higher proportion of AlCl₃ / [Bmim]Cl reduce the amount of yield as side products formed.

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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•AlCl₃ at 80 °C, 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; ¹HNMR(400MHz, CDCl₃) δ: 1.27 (t, 6H, 2 ×CH₃, J = 6.8 Hz), 2.31 (s, 6H, 2 ×CH₃), 4.21 (q, 4H, 2 ×CH₂O, J = 7.7 Hz), 5.03 (s, 1H, CH), 5.60 (s, 1H, NH), 7.30~7.49(m, 5H, ArH); Anal. Calcd for C₁₉H₂₃NO₄: 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; ¹HNMR(400MHz, CDCl₃) δ:1.29 (t, 6H, 2 ×CH₃, J = 6.8 Hz), 2.37(s, 6H, 2 ×CH₃), 4.33 (q, 4H, 2 ×CH₂O, J = 7.5 Hz), 5.21 (s, 1H, CH), 7.30~7.58(m, 4H, ArH), 8.77 (s, 1H, NH); Anal. Calcd for C₁₉H₂₂N₂O₆: C 60.95, H 5.92, N 7.48; found: C 60.89, H 5.89, N 7.42. 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; ¹HNMR (400MHz, CDCl₃) δ: 2.35 (s, 6H, 2 ×CH₃), 3.75 (s, 6H, 2 ×CH₃O), 4.99 (s, 1H, CH), 7.38-7.84 (m, 4H, ArH), 8.89(s, 1H, NH); Anal. Calcd for C₁₇H₂₁N₂O₆: C 58.96, H 5.24, N 8.09; found: C 58.91, H 5.22, N 8.02. 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; ¹HNMR(400MHz, CDCl₃) δ: 1.39(t, 6H, 2×CH₃, J= 6.8Hz), 2.41 (s, 6H, 2

×CH₃), 4.45 (q, 6H, 2 ×CH₂O, J=7.5Hz), 4.99 (s, 1H, CH), 7.58-7.94 (m, 4H, ArH), 8.91(s, 1H, NH); Anal. Calcd for C₁₉H₂₂N₂O₆: C 60.95, H 5.92, N 7.48; found: C 60.90, H 5.96, N 7.40. 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; ¹HNMR (400MHz, CDCl₃) δ: 2.26 (s, 6H, 2×CH₃), 3.55 (s, 6H, 2 ×CH₃O), 3.87(s, 3H, CH₃O), 5.01 (s, 1H, CH), 7.38-7.64 (m, 4H, ArH), 8.49(s, 1H, NH); Anal. Calcd for C₁₉H₂₁NO₅: 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; ¹HNMR (400MHz, CDCl₃) δ:1.13 (t, 6H, 2 ×CH₃, J = 6.8 Hz), 2.35 (s, 6H, 2 ×CH₃), 3.84 (s, 3H, CH₃O), 4.10 (q, 4H, 2 ×CH₂O, J = 7.5Hz), 5.07 (s, 1H, CH), 7.20-8.00 (M, 4H, ArH); 8.94(s, 1H, NH); Anal. Calcd for C₂₁H₂₅NO₅: 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; ¹HNMR (400MHz, CDCl₃) δ: 1.19 (d, 3H, J=6.4Hz), 1.29(t, 6H, 2×CH₂CH₃, J=6.8Hz), 2.32(s, 6H, 2×CH₃), 3.85(q, 1H, CH, J=6.0Hz),4.20(q, 6H, 2×CH₂O, J=7.2Hz), 5.56(s,1H, NH); Anal. Calcd for C₁₄H₂₁NO₄: 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; ¹HNMR (400MHz, CDCl₃) δ: 1.17(d, 3H, J=6.4Hz), 2.27(s, 6H, 2×CH₃), 3.45(s, 6H, 2×OCH₃), 3.85(q, 1H, CH, J=6.0Hz), 5.56(s, 1H, NH); Anal. Calcd for C₁₂H₁₇NO₄: C 60.24, H 7.16, N 5.85; found: C 60.20, H 7.13, N 5.81. 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; $^1\text{H-NMR}$ (400MHz, CDCl_3) δ : 1.29(t, 6H, $2\times\text{CH}_2\text{CH}_3$, $J=6.8\text{Hz}$), 2.32(s, 6H, $2\times\text{CH}_3$), 3.28(s, 2H, CH_2), 4.10(q, 4H, $2\times\text{CH}_2\text{O}$, $J=6.8\text{Hz}$), 5.48(s, 1H, NH); Anal. Calcd for $\text{C}_{19}\text{H}_{23}\text{NO}_4$: C 69.28, H 7.04, N 4.25; found: C 69.24, H 7.00, N 4.20. IR (KBr) ν : 3346, 3010, 1707, 1687, 1421, 1009 cm^{-1} .

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

Yellow crystals; $^1\text{H-NMR}$ (400MHz, CDCl_3) δ : 2.32(s, 6H, $2\times\text{CH}_3$), 3.28(s, 2H, CH_2), 3.86 (s, 3H, CH_3O), 5.53(s, 1H, NH); Anal. Calcd for $\text{C}_{11}\text{H}_{15}\text{NO}_4$: C 58.66, H 6.71, N 6.22; found: C 58.59, H 6.76, N 6.19. IR (KBr) ν : 3246, 3100, 1698, 1666, 1401, 1241, 909 cm^{-1} .

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

Yellow crystals; $^1\text{H-NMR}$ (400MHz, CDCl_3) δ : 1.30 (t, 6H, $2\times\text{CH}_2\text{CH}_3$, $J=6.7\text{Hz}$), 2.33(s, 6H, $2\times\text{CH}_3$), 4.18(q, 4H, $2\times\text{OCH}_2$, $J=6.8\text{Hz}$), 5.47(s, 1H, NH), 5.75(s, 1H, CH), 5.96(d, 1H, $\text{CH}=\text{C}$, $J=2.8\text{Hz}$), 6.23(t, 1H, $\text{CH}=\text{C}$, $J=3.2\text{Hz}$), 7.23(d, 1H, $\text{C}=\text{C}$, $J=4.2\text{Hz}$); Anal. Calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_5$: C 63.94, H 6.63, N 4.39; found: C 63.88, H 6.59, N 4.36. IR (KBr) ν : 3327, 3149, 1698, 1684, 1657, 1329, 1047 cm^{-1} .

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

Yellow crystals; $^1\text{H-NMR}$ (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 $\text{C}_{18}\text{H}_{21}\text{NO}_4$: C 68.55, H 6.71, N 4.44; found: C 68.59, H 6.74, N 4.44. IR (KBr) ν : 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; $^1\text{H-NMR}$ (CDCl_3): 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 $\text{C}_{18}\text{H}_{21}\text{NO}_4$: C 68.55, H 6.71, N 4.44; found: C 68.54, H 6.67, N 4.34. IR (KBr) ν : 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; $^1\text{H-NMR}$ (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 $\text{C}_{18}\text{H}_{21}\text{NO}_4$: C 68.55, H 6.71, N 4.44; found: C 68.54, H 6.68, N 4.38. IR (KBr) ν : 3315, 3250, 3049, 3023, 1698, 1655, 1496, 1381, 1341, 1316, 1305, 1243 cm^{-1} ;

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

$^1\text{H-NMR}$ (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 $\text{C}_{19}\text{H}_{23}\text{NO}_4$: C 69.28, H 7.04, N 4.25; found: C 69.30, H 7.02, N 4.22. IR (KBr) ν : 3371, 2990, 1688, 1655, 1148, 1121, 1096, 1051, 1020 cm^{-1} .

Conclusions

Ionic liquid $[\text{Bmim}]\text{Cl-AlCl}_3$ 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 be utilized for 5 times repeatedly with no decrease of the yield.

Acknowledgement

The authors express their thanks to the South-Central University for Nationalities for financial support during this investigation.

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