Highly efficient chemoselective construction of 2, 2-dimethyl-6-substituted-4-piperidone via multi-component tandem Mannich reaction in ionic liquids

Li-Chun Feng, Ya-Wei Sun, Wei-Jun Tang, Li-Jin Xu,* Kim Hung Lam, Zhongyuan Zhou, Albert S. C. Chan

a Department of Chemistry, Renmin University of China, Beijing 100872, China.
Email: xulj@chem.ruc.edu.cn;

b Open Laboratory of Chirotechnology of the Institute of Molecular Technology for Drug Discovery and Synthesis and Department of Applied Biology and Chemical Technology, the Hong Kong Polytechnic University, Hong Kong, China.

Table of Contents:

1. General information--------------------------------------------------------------- S2
2. General procedure for the tandem Mannich reactions in ionic liquid-----------S2
3. $^1$H and $^{13}$C NMR spectra of piperidones------------------------------------- S6
4. References --------------------------------------------------------------------- S20
1. General Information

Unless otherwise noted, all experiments were carried out under an atmosphere of nitrogen using standard Schlenk techniques or in a nitrogen-filled glovebox. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker Model Avance DMX 400 Spectrometer ( $^1$H 400 MHz and $^{13}$C 106.6 MHz, respectively). Chemical shifts (δ) are given in ppm and are referenced to residual solvent peaks. (S)-2, 2'-dihydroxy-1, 1'-binaphthyl-3-carbaldehyde was prepared according to the reported method. All other chemicals were used as received from Aldrich or Acros without further purification.

2. General procedure for the tandem Mannich reaction in ionic liquid

To a 10 mL sample vial charged with [bmim][PF$_6$] (1.0 mL) was added L-proline (0.2 mmol, 23 mg). To the mixture was bubbled in ammonia gas for 5 min. followed by the addition of aldehyde (1mmol) and acetone (10 mmol, 0.75 mL). The resulting mixture was allowed to stir at room temperature for 20 h. The excessive acetone was removed in vacuo and the residue was extracted with Et$_2$O (4 x 5mL). The combined extracts were dried over anhydrous Na$_2$SO$_4$, concentrated in vacuo. Purification on a silica gel column (eluting with n-hexane and ethyl acetate) gave the pure product.

2, 2-dimethyl-6-phenyl-4-piperidone (2a) (known compound)$^2$. $^1$H NMR (500 MHz, CDCl$_3$): δ = 7.41-7.39 (m, 2H), 7.36-7.33 (m, 2H), 7.29-7.26 (m, 1H), 4.20 (dd, $J$ = 3.5, 11.0 Hz, 1H), 2.50-2.39 (m, 3H), 2.27-2.24 (m, 1H), 1.60 (br, 1H), 1.31 (s, 3H), 1.19 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ = 209.8, 143.1, 129.0, 128.0, 126.8, 56.3, 54.5, 54.2, 50.0, 32.4, 25.6; HR-ESI: calcd. for C$_{13}$ H$_{18}$NO (M+H$^+$): 204.1388; found: 204.1385.

2, 2-dimethyl-6-(4'-fluorophenyl)-4-piperidone (2b). $^1$H NMR (500 MHz, CDCl$_3$): δ = 7.39-7.37 (m, 2H), 7.04-7.00 (m, 2H), 4.19 (dd, $J$ = 3.0, 11.5 Hz, 1H), 2.47-2.34 (m, 3H), 2.27-2.24 (m, 1H), 1.50 (br, 1H), 1.31 (s, 3H), 1.19 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ = 209.8, 143.1, 129.0, 128.0, 126.8, 56.3, 54.5, 54.2, 50.0, 32.4, 25.6; HR-ESI: calcd. for C$_{13}$ H$_{18}$NO (M+H$^+$): 204.1388; found: 204.1385.
2, 2-dimethyl-6-(4'-chlorophenyl)-4-piperidone (2c) $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.34-7.32 (m, 2H), 7.29-7.27 (m, 2H), 4.15 (dd, $J$ = 3.5, 11.0 Hz, 1H), 2.43-2.21 (m, 4H), 1.54 (br, 1H), 1.29 (s, 3H), 1.16 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 209.2, 141.8, 133.5, 129.0, 128.2, 55.6, 54.3, 54.1, 49.9, 32.3, 25.6; HR-ESI: calcd. for C$_{13}$H$_{17}$NOCl (M+H$^+$): 238.0999; found: 238.0991.

2, 2-dimethyl-6-(4'-bromophenyl)-4-piperidone (2d) $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.47-7.45 (m, 2H), 7.30-7.26 (m, 2H), 4.17 (dd, $J$ = 3.5, 11.0 Hz, 1H), 2.46-2.24 (m, 4H), 1.43 (br, 1H), 1.31 (s, 3H), 1.18 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 209.2, 142.3, 132.0, 128.6, 121.7, 55.7, 54.3, 54.2, 49.9, 32.4, 25.6; HR-ESI: calcd. for C$_{13}$H$_{17}$NO$^{79}$Br (M+H$^+$): 282.0494; found: 282.0496; HR-ESI: calcd. for C$_{13}$H$_{17}$NO$^{81}$Br (M+H$^+$): 284.0470.

2, 2-dimethyl-6-(4'-methoxyphenyl)-4-piperidone (2e) $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.32-7.30 (m, 2H), 6.87-6.85 (m, 2H), 4.14 (dd, $J$ = 4.0, 11.0 Hz, 1H), 3.77 (s, 3H), 2.43-2.22 (m, 4H), 1.62 (br, 1H), 1.29 (s, 3H), 1.17 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 210.0, 159.3, 135.3, 127.9, 114.3, 55.7, 55.5, 54.4, 54.1, 50.1, 32.4, 25.6; HR-ESI: calcd. for C$_{14}$H$_{20}$NO$_2$ (M+H$^+$): 234.1494; found: 234.1521.

2, 2-dimethyl-6-(3'-nitrophenyl)-4-piperidone (2f) $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 8.34 (s, 1H), 8.14-8.12 (m, 1H), 7.74 (d, $J$ = 7.0 Hz, 1H), 7.52 (t, $J$ = 8.0 Hz, 1H), 4.33 (dd, $J$ = 3.5, 11.5 Hz, 1H), 2.52-2.27 (m, 4H), 1.59 (br, 1H), 1.34 (s, 3H), 1.20 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 208.5, 148.8, 145.4, 133.2, 129.9, 123.1, 121.9, 55.6, 54.3, 54.2, 49.7, 32.3, 25.7; HR-ESI: calcd. for C$_{13}$H$_{17}$N$_2$O$_3$ (M+H$^+$): 249.1239; found: 249.1261.
2, 2-dimethyl-6-(1’-naphthyl)-4-piperidone (2g) \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 8.18 (d, J = 8.5 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 8.5 Hz, 1H), 7.75 (d, J = 7.0 Hz, 1H), 7.57-7.48 (m, 3H), 5.04 (dd, J = 3.5, 12.0 Hz, 1H), 2.72-2.36 (m, 4H), 1.61 (br, 1H), 1.36 (s, 3H), 1.35 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 210.0, 138.5, 134.2, 131.1, 129.3, 128.5, 126.6, 126.0, 125.9, 123.3, 123.0, 54.7, 54.4, 51.5, 48.9, 32.5, 25.6; HR-ESI: calcd. for C\(_{17}\)H\(_{20}\)NO (M+H\(^{+}\)): 254.1545; found: 254.1543.

2, 2-dimethyl-6-(2’-pyridyl)-4-piperidone (2h) \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 8.56-8.55 (m, 1H), 7.64 (dt, J = 2.0, 8.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.20-7.17 (m, 1H), 4.27 (dd, J = 4.5, 10.5 Hz, 1H), 2.56-2.32 (m, 4H), 2.19 (br, 1H), 1.34 (s, 3H), 1.16 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 210.0, 160.4, 149.8, 137.3, 123.0, 122.1, 57.7, 55.0, 54.9, 48.6, 32.1, 25.6; HR-ESI: calcd. for C\(_{12}\)H\(_{17}\)N\(_2\)O (M+H\(^{+}\)): 205.1341; found: 205.1339.

2, 2-dimethyl-6-(2’-furanyl)-4-piperidone (2i) \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.37-7.36 (m, 1H), 6.32-6.31 (m, 1H), 6.20 (d, J = 4.0 Hz, 1H), 4.32 (dd, J = 6.5, 9.0 Hz, 1H), 2.57-2.28 (m, 4H), 1.91 (br, 1H), 1.30 (s, 3H), 1.17 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 208.8, 155.1, 142.4, 110.4, 106.0, 54.7, 54.3, 50.1, 46.4, 32.0, 25.4; HR-ESI: calcd. for C\(_{11}\)H\(_{16}\)NO\(_2\) (M+H\(^{+}\)): 194.1181; found: 194.1190.

2, 2-dimethyl-6-(2’-ferrocenyl)-4-piperidone (2j) \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 4.23 (s, 2H), 4.20 (s, 2H), 4.14 (s, 5H), 3.93 (d, J = 12.0 Hz, 1H), 2.59-2.24 (m, 4H), 1.62 (br, 1H), 1.30 (s, 3H), 1.17 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 210.2, 91.8, 68.4, 68.1, 68.0, 66.6, 66.3, 54.7, 54.1, 51.1, 49.4, 32.4, 25.8; HR-ESI: calcd. for C\(_{17}\)H\(_{22}\)NOFe (M+H\(^{+}\)): 312.1051; found: 312.1058.

2, 2-dimethyl-6-cyclohexyl-4-piperidone (2k) \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 2.83-2.79 (m, 1H), 2.33-2.29 (m, 1H), 2.22-2.15 (m, 2H), 1.99-1.93 (m, 1H), 1.79-0.91 (m, 12H), 1.21 (s, 3H), 1.0 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta =
2, 2-dimethyl-6-pentyl-4-piperidone (2k) $^1$H NMR (500 MHz, CDCl$_3$): $\delta =$ 3.13-3.07 (m, 1H), 2.38-1.97 (m, 4H), 1.54-1.23 (m, 9H), 1.28 (s, 3H), 1.09 (s, 3H), 0.91-0.86 (m, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta =$ 210.3, 54.7, 54.4, 52.1, 48.2, 37.4, 32.1, 32.0, 25.7, 25.6, 22.8, 14.2; HR-ESI: calcd. for C$_{13}$H$_{24}$NO (M+H$^+$): 210.1858; found: 210.1862.

2, 2-dimethyl-6-(2'-hydroxyphenyl)-4-piperidone (2m) $^1$H NMR (500 MHz, CDCl$_3$): $\delta =$ 7.19-7.09 (m, 1H), 6.88-6.86 (m, 1H), 6.79-6.78 (m, 1H), 6.74-6.71 (m, 1H), 4.26 (dd, $J =$ 4.0, 12.5 Hz, 1H), 2.64-2.58 (m, 1H), 2.45-2.19 (m, 3H), 1.28 (s, 3H), 1.15 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta =$ 207.6, 157.2, 129.6, 127.4, 125.7, 119.8, 117.6, 56.1, 54.4, 53.6, 46.1, 32.2, 25.1; HR-ESI: calcd. for C$_{13}$H$_{18}$NO$_2$ (M+H$^+$): 220.1338; found: 220.1340.

2, 2-dimethyl-6-(4'-hydroxyphenyl)-4-piperidone (2n) $^1$H NMR (500 MHz, CDCl$_3$): $\delta =$ 7.26-7.17 (m, 2H), 6.73-6.68 (m, 2H), 4.16-4.13 (m, 1H), 2.56-2.25 (m, 4H), 1.32 (s, 3H), 1.21 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta =$ 210.3, 156.1, 134.0, 128.1, 116.0, 55.8, 54.5, 54.3, 49.5, 32.1, 25.5; HR-ESI: calcd. for C$_{13}$H$_{18}$NO$_2$ (M+H$^+$): 220.1338; found: 220.1332.

(S)-6-(2, 2'-dihydroxy-1, 1'-binaphthyl-3-yl)-2, 2-dimethylpiperidin-4-one (2o) $^1$H NMR (500 MHz, CDCl$_3$): $\delta =$ 7.80 (d, $J =$ 9.0 Hz, 1H), 7.95 (d, $J =$ 8.0 Hz, 1H), 7.90 (d, $J =$ 8.0 Hz, 1H), 7.79 (s, 1H), 7.45-7.32 (m, 5H), 7.25 (d, $J =$ 9.0 Hz, 1H), 7.21 (d, $J =$ 8.5 Hz, 1H), 4.75 (dd, $J =$ 4.0, 12.0 Hz, 1H), 3.01-2.96 (m, 1H), 2.54-2.36 (m, 2H), 1.34 (s, 3H), 1.33 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta =$ 206.8, 153.6, 151.5, 134.1, 133.8, 130.3, 129.5, 128.6, 128.5, 128.4, 128.3, 127.8, 127.7, 127.0, 124.9, 124.8, 124.4, 123.7, 117.9, 114.8, 114.7, 56.2, 55.0, 53.4, 46.0, 31.7, 25.0; $[\alpha]^{20}_D =$ -
117 (c = 10 mg/mL, CH$_2$Cl$_2$); HR-ESI: calcd. for C$_{27}$H$_{25}$NO$_3$ (M+H$^+$): 412.1913; found: 412.1907.

3. $^1$H and $^{13}$C NMR spectra of piperidones
4. Reference
