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A facile synthesis of 3-(substituted benzyl)piperidines

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Abstract—A convenient new method has been developed for preparation a series of 3-(substituted benzyl)piperidines by addition of substituted phenylmagnesium bromide to pyridine-3-carboxaldehyde followed by one pot deoxygenation and heteroaromatic ring saturation in the presence of palladium catalyst.

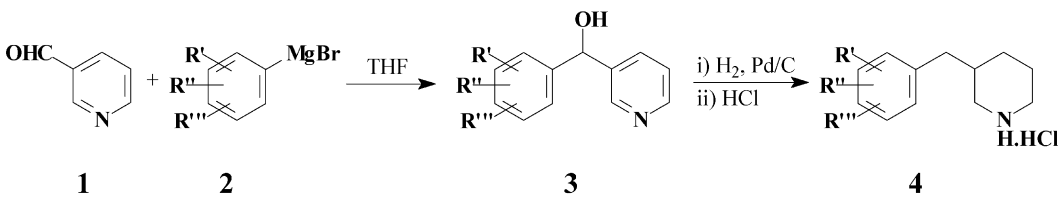
1. Introduction

Benzylpiperidines and their derivatives possess a range of physiological and pharmaceutical activities. Substituted 4-benzylpiperidines exhibit *N*-methyl-D-aspartate (NMDA) antagonist activity,[1] as well as high affinity for other central nervous system receptors.[2] 2-Benzylpiperidine derivatives are known dopamine receptor antagonists,[3] while the 3-benzylpiperidines show fungicide activity.[4] Numerous multistep syntheses are described in the literature for preparation of this important class of compounds but the overall yields are usually low and exotic reagents or conditions are used in many cases. Thus, 3-benzylpiperidine was synthesized from 2-piperidone by successive lithiation, benzylation and hydride reduction sequence.[4] In other processes 3-benzoylpyridine was deoxygenated with hydrogen iodide and phosphorous then the pyridine ring was reduced with sodium in alcohol[5] or the same starting material was converted into the target molecule via nickel catalysed reduction at high pressure and temperature.[6] However, synthesis of 3-benzoylpyridine requires special reagents (naphthalene–lithium or activated zinc,[7,8] trimethylstannylpyridine,[9] homogenous palladium catalyst and carbon monoxide[10]), too. In other methods, aryl-3-pyridylmethanols were synthesized via organometallic intermediates[11–14] then deoxygenated using iodotrimethylsilane[12,13] or samarium iodide[15] to get 3-(substituted benzyl)pyridines or the formed pyridylmethanol was oxidated to ketone, an intermediate of alkylidene derivatives of 3-benzylpiperidine.[14] Saturation of the pyridine ring has usually been carried out in a separate hydrogenation reaction in the presence of platinum,[16] platinum oxide,[15] palladium[17] or Raney-nickel[18] catalysts.

2. Results and discussion

Here, we report a novel, short and efficient synthesis of 3-(substituted benzyl)piperidines starting from readily pyridine-3-carboxaldehyde (**1**) and Grignard reagents prepared from mono-, di-, or trisubstituted bromobenzenes (**2a–i**) and continued by a one-pot catalytic deoxygenation and heteroaromatic ring saturation of the aryl-3-pyridylmethanol intermediates (**3a–i**, Scheme 1).

Addition of **1** to the Grignard-reagents provided **3a–i** in moderate to good yields (Table 1). The crude products were dissolved in glacial acetic acid and hydrogenated in the presence of 10% Pd/C (Montecatini) catalyst. Conditions of the deoxygenation–saturation reaction are listed in Table 1.



1 **2** **3** **4**

Scheme 1.

Keywords: Grignard-reaction; catalytic reduction; catalytic deoxygenation; 3-benzylpiperidine.
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Table 1. Preparation of 3-(substituted phenyl)methylpiperidines

Starting material		Intermediate		Hydrogenation		Product	
No.	Substituents (R′,R″,R‴)	No.	Yield (%)	Pressure (bar)	Temperature (°C)	No.	Yield (%)
2a	4-CH_3O	**3a**	68	8	70	**4a**	76
2b	2-CH_3O	**3b**	67	10	80	**4b**	91
2c	4-F	**3c**	83	10	80	**4c**[a]	76
2d	3,5-$(CH_3)_2$-4-CH_3O	**3d**	82	10	80	**4d**	75
2e	3,4-$(CH_3O)_2$	**3e**	74	10	75	**4e**	82
2f	3-CF_3	**3f**	86	10	75	**4f**[a]	70
2g	4-CH_3	**3g**	83	10	60	**4g**	89
2h	4-[CH_2=$C(CH_3)CH_2O$]	**3h**	60	10	80	**5**[a]	62
2i	4-$PhCH_2O$	**3i**	54	1	30	**6**[b]	61

[a] Isolated as base by vacuum distillation.
[b] Prepared in the presence of sulfuric acid, isolated as hydrogensulfate salt.

The products (**4a**–**g**) were isolated as hydrochloride salts in crystalline form. Yields given in Table 1 refer to the isolated pure products.

In the case of **3h** saturation of the double bond in the side chain occurred parallel with the ring saturation. Thus, we obtained 3-(4-isobutoxyphenyl)methylpiperidine hydrochloride (**5**). This reaction is a new, simple route to compound **5** (**2h** can easily be obtained from 4-bromophenol and cheap β-methallyl chloride).

Selective debenzylation of **3i** was also accomplished under mild conditions (atmospheric pressure, 30°C, methanol/H_2SO_4) yielding 3-(4-hydroxyphenyl)methylpyridine (**6**). The free hydroxy group is useful for elaboration to further *O*-alkyl derivatives of **6** before pyridine ring saturation and this route is much smoother than demethylation of the corresponding methoxy derivative.

3. Conclusions

On the basis of these results we have found this two step procedure to be simple to accomplish, inexpensive, high-yielding and benign even on multigram scale. Extended studies on the scopes and applications of this method are currently underway.

4. Experimental

4.1. General

All commercial starting materials were purchased from FLUKA AG and Merck-Schuchardt and were used without further purification. Tetrahydrofuran were obtained anhydrous by distillation from sodium wire after the characteristic blue color of in situ generated sodium diphenylketyl had been found to persist. All Grignard-reactions were carried out under dry nitrogen atmosphere.

^{1}H NMR spectra were recorded in hexadeuteriodimethylsulfoxide or deuteriochloroform solution at 300 and 500 MHz (Varian Innova Spectrometers). Chemical shifts refer to tetramethylsilane (δ 0 ppm), coupling constants are given in Hz. Melting point were determined using Büchi capillary melting point apparatus. IR spectra of solids were recorded as KBr pellets, and IR spectra of oils were recorded as thin films on NaCl plates with a Perkin–Elmer Spectrum 1000 FT-IR spectrophotometer.

4.2. General procedure for the preparation of aryl-3-pyridyl-methanol 3

At 20°C, a solution of **1** (200 mmol, 18.9 ml) in tetrahydrofuran (100 ml) was added to the Grignard-reagent prepared from **2a**–**i** (210 mmol) and magnesium turnings (205 mmol, 4.94 g) in tetrahydrofuran (300 ml). After 10 h stirring, 80 ml saturated ammonium chloride solution was poured into the reaction mixture, the phases were separated, the tetrahydrofuran solution was dried and concentrated in vacuo. The residue was treated with hexane or ethyl acetate to get carbinol **3a**–**i**.

4.2.1. 4-Methoxyphenyl-3-pyridyl-methanol 3a. Pale yellow solid; mp 104–105°C (lit.[19] mp 106–107°C); IR (KBr pellets, cm^{-1}) ν_{max} 3190, 1515, 1251, 1172, 1031, 806; ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 3.76 (s, 3H), 4.57 (s, br, 1H), 5.75 (s, 1H), 6.84 (m, 2H), 7.17 (m, 1H), 7.22 (m, 2H), 7.66 (m, 1H), 8.29 (m, 1H), 8.43 (m, 1H). Anal. calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.42; H, 6.19; N, 6.37.

4.2.2. 2-Methoxyphenyl-3-pyridyl-methanol 3b. Pale yellow solid; mp 112°C; IR (KBr pellets, cm^{-1}) ν_{max} 3151, 1586, 1490, 1439, 1241, 1047, 1029, 760; ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 3.76 (s, 3H), 3.93 (s, br, 1H), 6.07 (s, 1H), 6.86 (d, J=8.5 Hz, 1H), 6.96 (m, 1H), 7.20 (m, 1H), 7.26 (m, 1H), 7.34 (m, 1H), 7.70 (m, 1H), 8.37 (m, 1H), 8.54 (d, J=1.5 Hz, 1H). Anal. calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.65; H, 6.01; N, 6.39.

4.2.3. 4-Fluorophenyl-3-pyridyl-methanol 3c. Pale yellow solid; mp 150°C (lit.[20] mp of hydrochloride salt 158.3°C); IR (KBr pellets, cm^{-1}) ν_{max} 3204, 1602, 1508, 1222, 1060, 811, 685, 565; ^{1}H NMR (DMSO, 500 MHz) δ ppm 6.10 (s, 1H), 7.20 (m, 2H), 7.52 (m, 2H), 8.05 (m, 1H), 8.55 (d, J=8.0 Hz, 1H), 8.86 (d, J=8.0 Hz, 1H), 8.96 (t, J=1.0 Hz, 1H). Anal. calcd for $C_{12}H_{10}FNO$: C, 76.18; H, 5.33; N, 7.40. Found: C, 76.29; H, 5.21; N, 7.31.

4.2.4. 3,5-Dimethyl-4-methoxyphenyl-3-pyridyl-methanol 3d. Pale yellow solid; mp 96–97°C; IR (KBr pellets, cm^{-1}) ν_{max} 3188, 1476, 1224, 1143, 1059, 1012, 714; ^{1}H

NMR (DMSO, 500 MHz) δ ppm 2.19 (s, 6H), 3.60 (s, 3H), 5.66 (d, J=4.0 Hz, 1H), 5.92 (d, J=4.0 Hz, 1H), 7.03 (s, 2H), 7.31 (m, 1H), 7.71 (m, 1H), 8.41 (m, 1H), 8.57 (d, J=2.0 Hz, 1H). Anal. calcd for $C_{15}H_{17}NO_2$: C, 74.07; H, 7.04; N, 5.76. Found: C, 73.91; H, 7.16; N, 5.60.

4.2.5. 3,4-Dimethoxyphenyl-3-pyridyl-methanol 3e. Pale yellow solid; mp 98–99°C (lit.[21] no data); IR (KBr pellets, cm^{-1}) ν_{max} 3154, 1592, 1515, 1270, 1228, 1136, 1026; ^1H NMR ($CDCl_3$, 500 MHz) δ ppm 3.80 (s, 3H), 3.84 (s, 3H), 4.56 (s, br, 1H), 5.76 (s, 1H), 6.78–6.86 (m, 2H), 6.88 (d, J=2.0 Hz, 1H), 7.20 (m, 1H), 7.67 (m, 1H), 8.32 (m, 1H), 8.48 (d, J=2.0 Hz, 1H). Anal. calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.39; H, 6.03; N, 5.54.

4.2.6. 3-(Trifluoromethyl)phenyl-3-pyridyl-methanol 3f. Colorless oil; bp 134–138°C/0.1 mm Hg (lit.[19] no data); IR (film, cm^{-1}) ν_{max} 3169, 1427, 1330, 1164, 1123, 1073, 799, 704; ^1H NMR ($CDCl_3$, 500 MHz) δ ppm 5.81 (s, br, 1H), 6.42 (s, br, 1H), 7.18 (m, 1H), 7.39 (m, 1H), 7.45–7.52 (m, 2H), 7.64–7.70 (m, 2H), 8.20 (m, 1H), 8.34 (m, 1H). Anal. calcd for $C_{13}H_{10}F_3NO$: C, 61.66; H, 3.98, N, 5.53. Found: C, 61.81; H, 4.09; N, 5.61.

4.2.7. 4-Tolyl-3-pyridyl-methanol 3g. Pale yellow solid; mp 132–133°C (lit.[22] mp 130–132°C); IR (KBr pellets, cm^{-1}) ν_{max} 3155, 2855, 1425, 1061, 1040, 1028, 801; ^1H NMR ($CDCl_3$, 500 MHz) δ ppm 2.33 (s, 3H), 3.70 (s, br, 1H), 5.79 (s, 1H), 7.26–7.10 (m, 5H), 7.68 (m, 1H), 8.35 (dd, J=4.8, 1.8 Hz, 1H), 8.49 (d, J=2.4 Hz, 1H). Anal. calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.84. Found: C, 78.19; H, 6.35; N, 7.97.

4.2.8. 4-(2-Methylallyloxy)phenyl-3-pyridyl-methanol 3h. Pale yellow solid; mp 115–116°C; IR (KBr pellets, cm^{-1}) ν_{max} 3148, 2854, 1610, 1513, 1426, 1235, 1172, 1060, 1016; ^1H NMR ($CDCl_3$, 500 MHz) δ ppm 1.81 (s, 3H), 4.00 (s, br, 1H), 4.41 (s, 2H), 4.97 (s, 1H), 5.07 (s, 1H), 5.77 (s, 1H), 6.87 (m, 2H), 7.17–7.25 (m, 3H), 7.67 (m, 1H), 8.34 (dd, J=5.0, 1.5 Hz, 1H), 8.48 (d, J=2.0 Hz, 1H). Anal. calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 3.58. Found: C, 75.42; H, 6.87; N, 3.76.

4.2.9. 4-Benzyloxyphenyl-3-pyridyl-methanol 3i. Pale yellow solid; mp 161–162°C; IR (KBr pellets, cm^{-1}) ν_{max} 3141, 1608, 1510, 1243, 1232, 1005, 748; ^1H NMR (DMSO, 300 MHz) δ ppm 5.07 (s, 2H), 5.72 (d, J=6.5 Hz, 1H), 5.95 (d, J=6.5 Hz, 1H), 6.96 (m, 2H), 7.25–7.46 (m, 8H), 7.70 (m, 1H), 8.41 (dd, J=4.5, 1.2 Hz, 1H), 8.57 (d, J=1.5 Hz, 1H). Anal. calcd for $C_{19}H_{11}NO_2$: C, 79.99; H, 3.89; N, 4.91. Found: C, 80.08; H, 3.98; N, 5.09.

4.3. General procedure for hydrogenation

In an autoclave, a mixture of 10% Pd/C catalyst (3 g) and acetic acid solution (250 ml) of **3a–i** (100 mmol) was hydrogenated (pressure and temperature are given in Table 1) until consumption of the hydrogen gas stopped. The catalyst was filtered off, the solution was concentrated in vacuo then the residue was solved in 20% hydrochloric acid (20 ml) and concentrated again in vacuo. Treatment of the acetic acid free residue with acetone or diethyl ether (150 ml) gave the corresponding piperidine hydrochloride derivative (**4a–g**) in pure form.

4.3.1. 3-(4-Methoxyphenyl)methylpiperidine hydrochloride 4a. White solid; mp 165°C (lit.[4] no data); IR (KBr pellets, cm^{-1}) ν_{max} 3423, 2938, 2507, 2403, 1512, 1240, 1180, 1028; ^1H NMR (DMSO, 500 MHz) δ ppm 1.16 (m, 1H), 1.55–1.76 (m, 3H), 1.96 (m, 1H), 2.46–2.53 (m, 3H), 2.70 (m, 1H), 3.02 (m, 1H), 3.14 (m, 1H), 3.73 (s, 3H), 6.85 (m, 2H), 7.10 (m, 2H), 9.15 (br, s, 2H). Anal. calcd for $C_{13}H_{20}ClNO$: C, 64.58; H, 8.34; N, 5.79; Cl, 14.66. Found: C, 64.36; H, 8.17; N, 5.88; Cl, 14.42.

4.3.2. 3-(2-Methoxyphenyl)methylpiperidine hydrochloride 4b. White solid; mp 158°C (lit.[23] no data); IR (KBr pellets, cm^{-1}) ν_{max} 3435, 2937, 2510, 2400, 1495, 1459, 1438, 1245, 1024; ^1H NMR (DMSO, 500 MHz) δ ppm 1.20 (m, 1H), 1.54–1.78 (m, 3H), 2.02 (m, 1H), 2.47–2.58 (m, 3H), 2.72 (m, 1H), 3.00 (m, 1H), 3.15 (m, 1H), 3.78 (s, 3H), 6.88 (m, 1H), 6.98 (d, J=8.5 Hz, 1H), 7.11 (d, J=8.4 Hz, 1H), 7.21 (d, 1H), 8.95 (s, br, 2H). Anal. calcd for $C_{13}H_{20}ClNO$: C, 64.74; H, 8.45; N, 5.61; Cl, 14.72. Found: C, 64.36; H, 8.17; N, 5.88; Cl, 14.42.

4.3.3. 3-(4-Fluorophenyl)methylpiperidine 4c. Colorless oil; bp 76°C/0.1 mm Hg (lit.[24] no data); IR (film, cm^{-1}) ν_{max} 3304, 2928, 1601, 1510, 1415, 1276, 1221, 1156; ^1H NMR ($CDCl_3$, 300 MHz) δ ppm 1.05 (m, 1H), 1.39 (m, 1H), 1.58–1.80 (m, 4H), 2.27 (dd, J=10.2, 12.0 Hz, 1H), 2.36–2.58 (m, 3H), 2.92–3.02 (m, 2H), 6.94 (m, 2H), 7.07 (m, 2H). Anal. calcd for $C_{12}H_{16}FN$: C, 74.57; H, 8.34; N, 7.25. Found: C, 74.72; H, 8.11; N, 7.38.

4.3.4. 3-(3,5-Dimethoxy-4-methylphenyl)methylpiperidine hydrochloride 4d. White solid; mp 180°C; IR (KBr pellets, cm^{-1}) ν_{max} 3428, 2949, 2538, 2412, 1444, 1227, 1148, 1013; ^1H NMR (DMSO, 500 MHz) δ ppm 1.16 (m, 1H), 1.55–1.77 (m, 3H), 1.93 (m, 1H), 2.19 (s, 6H), 2.38–2.45 (m, 2H), 2.50 (m, 1H), 2.70 (m, 1H), 3.03 (m, 1H), 3.16 (m, 1H), 3.62 (s, 3H), 6.82 (s, 2H), 8.94 (s, br, 2H). Anal. calcd for $C_{15}H_{24}ClNO_2$: C, 63.04; H, 9.14; N, 4.90; Cl, 12.40. Found: C, 62.91; H, 9.22; N, 4.75; Cl, 12.51.

4.3.5. 3-(3,4-Dimethoxyphenyl)methylpiperidine hydrochloride 4e. White solid; mp 158°C; IR (KBr pellets, cm^{-1}) ν_{max} 3434, 2937, 2528, 2418, 1524, 1263, 1142, 1021; ^1H NMR (DMSO, 500 MHz) δ ppm 1.18 (m, 1H), 1.54–1.80 (m, 3H), 1.99 (m, 1H), 2.42–2.56 (m, 3H), 2.71 (m, 1H), 3.01 (m, 1H), 3.16 (m, 1H), 3.72 (s, 3H), 3.74 (s, 3H), 6.68 (dd, J=13.5, 3.5 Hz, 1H), 6.79 (d, J=3.5 Hz, 1H), 6.87 (d, J=13.5 Hz, 1H), 8.92 (s, br, 1H), 9.18 (s, br, 1H). Anal. calcd for $C_{14}H_{22}ClNO_3$: C, 58.43; H, 7.70; N, 4.87; Cl, 12.32. Found: C, 58.32; H, 7.93; N, 4.62; Cl, 12.08.

4.3.6. 3-(3-Trifluoromethylphenyl)methylpiperidine 4f. Colorless oil; bp 116–118°C/0.1 mm Hg; IR (film, cm^{-1}) ν_{max} 3291, 2930, 1450, 1334, 1164, 1125, 1074, 806, 704; ^1H NMR ($CDCl_3$, 500 MHz) δ ppm 1.09 (m, 1H), 1.42 (m, 1H), 1.64 (m, 1H), 1.68–1.78 (m, 2H), 1.86 (s, br, 1H), 2.30 (dd, J=10.2, 12.0 Hz, 1H), 2.48–2.58 (m, 3H), 2.93–3.02 (m, 2H), 7.29–7.46 (m, 4H). Anal. calcd for $C_{13}H_{16}F_3N$: C, 64.20; H, 6.63; N, 5.76. Found: C, 64.05; H, 6.86; N, 5.81.

4.3.7. 3-(4-Tolyl)methylpiperidine hydrochloride 4g. White solid; mp 174°C (lit.[4] no data); IR (KBr pellets, cm^{-1}) ν_{max} 3408, 2945, 2511, 2404, 1516, 1446; ^1H NMR ($CDCl_3$, 300 MHz) δ ppm 1.12 (m, 1H), 1.74–1.89 (m, 3H), 2.25 (m, 1H), 2.30 (s, 3H), 2.42–2.61 (m, 3H), 2.70 (m, 1H), 2.24–2.44 (m, 2H), 6.99–7.09 (m, 4H), 9.32 (s, br, 1H), 9.60 (s, br, 1H). Anal. calcd for $C_{13}H_{20}ClN$: C, 69.16; H, 8.93; N, 6.20; Cl, 15.70. Found: C, 68.92; H, 8.75; N, 6.01; Cl, 15.78.

4.3.8. 3-(4-Isobutoxyphenyl)methylpiperidine 5. Colorless oil; bp 124–126°C/0.2 mm Hg (lit.[23] no data); IR (film, cm^{-1}) ν_{max} 3299, 2928, 1612, 1512, 1471, 1244, 1174, 1037; ^1H NMR ($CDCl_3$, 300 MHz) δ ppm 1.00 (d, J=6.6 Hz, 6H), 1.10 (m, 1H), 1.40 (m, 1H), 1.55–1.70 (m, 2H), 1.75 (m, 1H), 2.02 (s, br, 1H), 2.06 (m, 1H), 2.26 (dd, J=10.2, 12.0 Hz, 1H), 2.32–2.47 (m, 2H), 2.51 (m, 1H), 2.96 (m, 2H), 3.68 (d, J=6.6 Hz, 1H), 6.80 (m, 2H), 7.02 (m, 2H). Anal. calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.52; H, 10.28; N, 5.54.

4.3.9. 3-(4-Hydroxyphenyl)methylpyridine hydrogensulfate 6. White solid; mp 102°C; IR (KBr pellets, cm^{-1}) ν_{max} 3291, 2785, 1553, 1512, 1211, 1171, 1068, 1004; ^1H NMR (DMSO, 300 MHz) δ ppm 4.06 (s, 2H), 6.66–6.78 (m, 2H), 7.04–7.16 (m, 2H), 7.98 (dd, J=8.1, 5.7 Hz, 1H), 8.40 (d, J=8.1 Hz, 1H), 8.77 (d, J=5.7 Hz, 1H), 8.82 (s, 1H), 9.40–10.10 (s, br, 3H). Anal. calcd for $C_{12}H_{13}NO_5S$: C, 50.89; H, 4.63; N, 4.94; S, 11.32. Found: C, 51.08; H, 4.87; N, 5.09; S, 11.61.

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