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Controlling chemoselective transformations of 4-acylpyridines via a Pd–C catalytic hydrodechlorination–hydrogenation

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ABSTRACT

A novel Pd–C catalytic hydrodechlorination–hydrogenation was developed for a multi-step one-pot transformation of 4-acylpyridines. Under the selected conditions, 4-benzoylpyridines and 4-alkanoylpyridines were chemoselectively converted into the corresponding 4-benzylpiperidine hydrochlorides and α-alkyl-4-piperidinemethanol hydrochlorides, respectively. This catalytic method was performed simply by an addition of 1 equiv of $ClCH_2CHCl_2$ to the conventional hydrogenation system and directly gave the crystalline piperidine hydrochlorides in practical quantitative yields.

1. Introduction

4-Benzylpiperidines (**1**) have been gaining importance due to them having been recognized as both key pharmacophores and intermediates in drug discovery. As shown in Fig. 1, many promising drug candidates contain this structural unit, such as TAK 220 (**2**),[1] ifenprodil (**3**),[2] and eliprodil (**4**).[3]

Investigation showed that 4-benzylpiperidines (**1**) normally were prepared starting from 4-piperidone[4] or 4-methylene-piperidine[4g,5] by various four-step methods. However, they also could be prepared starting from 4-benzoylpyridines (**5**) in a single flask by a Pd–C catalytic hydrogenation.[6] Although the hydrogenation method was associated with certain drawbacks related to efficiency, separation, and purification, it represented a streamlined, inexpensive, and scalable process.

Herein, we report a novel Pd–C catalytic hydrodechlorination–hydrogenation of 4-acylpyridines. Under the selected pressure or temperature, the controlling chemoselective transformations were achieved depending upon the substrate structures. As shown in Scheme 1, this new catalytic system can be established simply by adding 1 equiv of $ClCH_2CHCl_2$ to the conventional hydrogenation system. In a single flask, 4-benzoylpyridines (**5**) and 4-alkanoylpyridines (**6**) were converted into the corresponding crystalline 4-benzylpiperidine hydrochlorides (**1**·**HCl**) and α-alkyl-4-piperidinemethanol hydrochlorides (**7**·**HCl**) in practical quantitative yields.

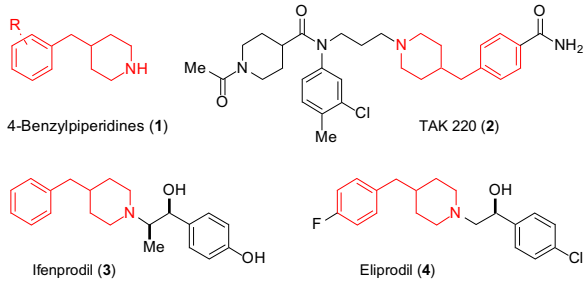
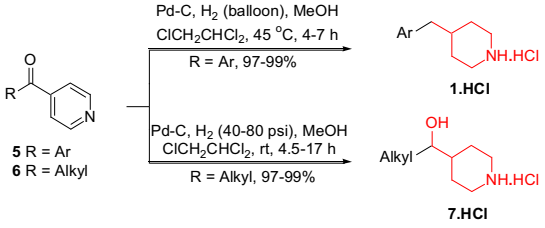


Fig. 1. 4-Benzylpiperidines (**1**) and the promising drug candidates **2**–**4**.



Scheme 1.

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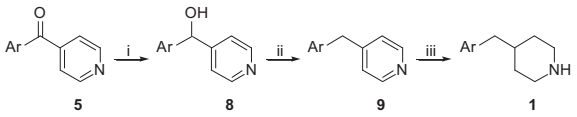
2. Results and discussion

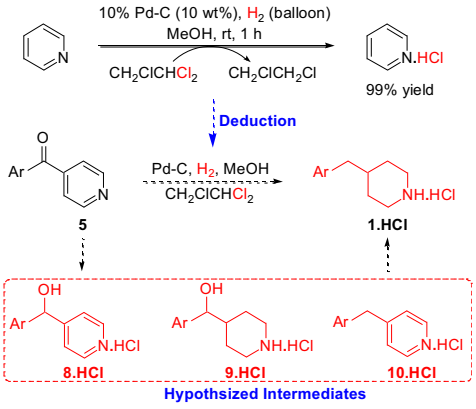
As shown in Scheme 2, the reported hydrogenations[6] of 4-benzoylpyridines (**5**) in literature have proved to be a three-step one-pot process: (i) a reduction of the ketone in **5**; (ii) a hydrogenolysis of the C–O bond in **8**; (iii) a hydrogenation of the pyridine nucleus in **9**. Since Pd–C is a preferred catalyst for the reduction of aryl ketone and the hydrogenolysis of benzyl alcohol, both step i and step ii can be carried out smoothly. But, Pd–C is a weak catalyst (compared with Pt-based catalysts) for the hydrogenation of pyridine nucleus in step iii.[7] Therefore, development of an efficient Pd–C catalytic hydrogenation of pyridine nucleus is a key issue for the efficient conversion of **5** into **1**.



Scheme 2.

It is well known that the *N*-atoms in the substrate pyridine and the product piperidine can strongly coordinate with the catalyst to lead an ineffective hydrogenation of pyridine nucleus.[7] However, it has been well recognized that this problem can be solved easily by using the isolated pyridine salts as substrates.[8] For example, pyridine hydrochloride can be hydrogenated to give piperidine hydrochloride in quantitative yield under room temperature and atmospheric pressure, in which all *N*-atoms were masked completely as their amine hydrochlorides. However, this strategy was seldom used[9] because preparation of the isolated pyridine salts is a tough task due to their highly hygroscopic properties.[10] Alternatively, the hydrogenation of pyridines was typically carried out in the presence of HOAc, aq HCl or aq H_2SO_4.[11] But low efficiencies were observed in many cases caused by incomplete formation of pyridine salts, by which the catalyst could be coordinated by free pyridines and also be poisoned by free acids. Ideally, the pyridine salts can be formed stoichiometrically in situ during the catalytic hydrogenation.

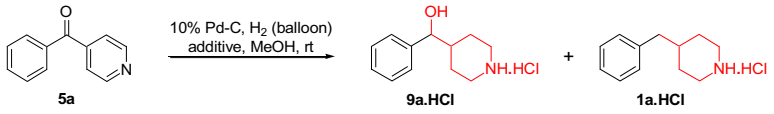
8·HCl, **9·HCl**, and **10·HCl** may be produced when 4-benzoylpyridine (**5**) is hydrogenated in the presence of $ClCH_2CHCl_2$. Finally, they will be converted into 4-benzylpiperidine hydrochloride (**1·HCl**) through different pathways under mild conditions.



Scheme 3.

Thus, 4-benzoylpyridine (**5a**) was used as a model substrate for conditional tests. As shown in Table 1, an inseparable mixture was produced when the suspension of **5a** and 10% Pd–C (100 wt %) in MeOH was hydrogenated under the conventional conditions (entry 1). No improvement was observed by addition of aq HCl as an additive (entry 2). To our delight, the expected crystalline **1a·HCl** was collected as a single product in 99% yield within 3 h in the presence of $ClCH_2CHCl_2$ (entry 3). The satisfactory result was also obtained by using 75 wt % of Pd–C (entry 4), but a mixture of **1a·HCl** and **9a·HCl** was obtained by using less than 50 wt % of Pd–C (entry 5). The proportion of **1a·HCl** decreased as the amount of Pd–C decreased (entry 6).

Table 1
Hydrogenation of **5a** in the presence of $ClCH_2CHCl_2$



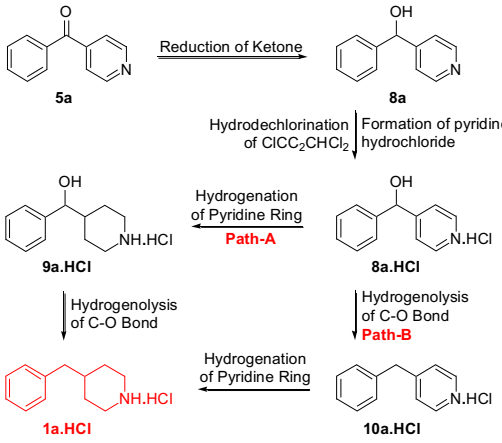
Entry	10% Pd–C (wt %)	Additive (equiv)	Time (h)	**9a·HCl**/**1a·HCl**[a] (%)	Yield[b] (%)
1	100	None	24	Inseparable mixture	—[c]
2	100	37% aq HCl (1.0)	24	Inseparable mixture	—[c]
3	100	$ClCH_2CHCl_2$ (1.2)	3	0:100	99
4	75	$ClCH_2CHCl_2$ (1.2)	11	0:100	99
5	50	$ClCH_2CHCl_2$ (1.2)	24	11:89	99
6	25	$ClCH_2CHCl_2$ (1.2)	40	37:63	99

[a] The ratio was measured by ^{1}H NMR.
[b] The isolated yields were obtained.
[c] The substrate **5a** was not exhausted.

In our recent works, an amine promoted Pd–C catalytic hydrodechlorination of geminal dichloroalkanes was discovered.[12] Its chemoselectivity was controlled so well that the amine hydrochlorides were formed stoichiometrically.[12a] As shown in Scheme 3, we luckily found that the pyridine hydrochloride can be quantitatively produced in situ in a Pd–C catalytic hydrodechlorination of $CH_2ClCHCl_2$ (it was used specifically for its inexpensive price) when pyridine was used as an amine. Since no free *N*-atoms and free HCl molecules were presented in this process, the catalytic activity of Pd–C was never decreased. Thus, we hypothesized that three possible intermediates

By carefully monitoring the hydrogenation in entry 5 (Table 1), we found that **5a** was reduced into **8a** completely in the first 5 min. Since the pyridine ring in **8a** was not conjugated with ketone, its base strength increased significantly. As shown in Scheme 4, **8a** (as a base) promoted hydrodechlorination of $ClCH_2CHCl_2$ then started to form **8a·HCl**. Furthermore, **8a·HCl** was converted into the final product **1a·HCl** through two competitive pathways. In path-A, its pyridine nucleus was hydrogenated first followed by a hydrogenolysis of the C–O bond. In path-B, its C–O bond was hydrogenolyzed first followed by a hydrogenation of the pyridine

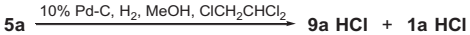
nucleus. Since the conditional experiments proved that the pure **9a·HCl** could be converted into **1a·HCl** in only 21% yield under the same conditions, it indicated that path-A is unfavorable pathway for the conversion of **8a·HCl** into **1a·HCl**. This result was caused clearly by the fact that **9a·HCl** is a monoaryl substituted benzyl alcohol and the hydrogenolysis of its C–O bond is much more difficult than that of **8a·HCl** (as a diaryl substituted benzyl alcohol). This may be also the reason that **9a·HCl** was isolated as a by-product when low proportions of Pd–C were employed (entries 5 and 6, Table 1). Thus, path-B should be the main path and the whole procedure was a five-step, one-pot process including: (i) a fast reduction of the ketone in **5a**; (ii) a pyridine-controlled chemoselective hydrodechlorination of $ClCH_2CHCl_2$; (iii) an in situ formation of pyridine hydrochloride (**8a·HCl**); (iv) a hydrogenolysis of the C–O bond in **8a·HCl**; (v) a hydrogenation of pyridine hydrochloride (**10a·HCl**).



Scheme 4.

As shown in Table 2, the intermediate **9a·HCl** can be exhausted by elevating the pressure or temperature when low proportions of Pd–C were used. For an efficient laboratory-scale operation, we preferred to choose entry 4 as our standard conditions.

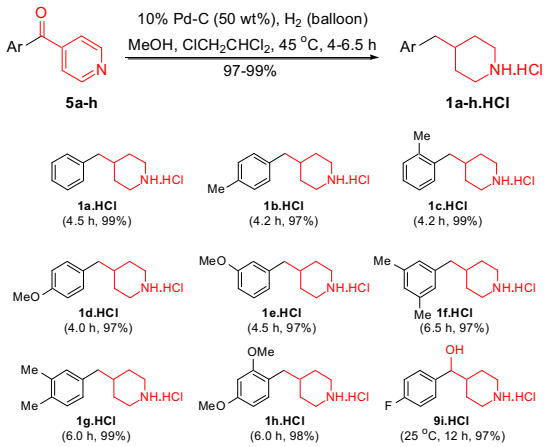
Table 2
Hydrogenation of **5a** in the presence of $ClCH_2CHCl_2$



Entry	10% Pd–C (wt %)	Pressure (psi)	Temp (°C)	Time (h)	**9a·HCl/1a·HCl**[a] (%)	Yield[b] (%)
1	50	40	25	23	60:40	99
2	50	80	25	11	0:100	99
3	50	Balloon	35	12	0:100	99
4	50	Balloon	45	4.5	0:100	99
5	25	Balloon	35	30	0:100	99
6	25	Balloon	45	12	0:100	99
7	10	Balloon	45	22	6:94	99

[a] The ratio was measured by ^1H NMR.
[b] The isolated yields were obtained.

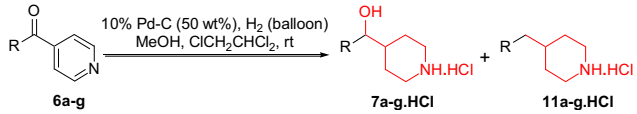
As shown in Scheme 5, all substrates **5a–h** were hydrogenated into the corresponding **1a–h·HCl** in practical quantitative yields under the standard conditions. But, the substrates bearing electron-withdrawing group on the benzene ring resisted the complete hydrogenolysis of the C–O bond. Thus, **9i·HCl** was obtained as a single product from the substrate **5i** at room temperature.



Scheme 5.

When this method was extended to 4-alkanoylpyridines (**6**), interesting results were observed under room temperature and atmospheric pressure. As shown in Table 3, 4-pyridinemethanol hydrochloride derivatives (**7·HCl**) were obtained as major products from the short-chain substrates (entries 1–5) and their proportions increased as the chain length increased. When the chain length was longer than 6-carbon, the crystalline **7·HCl** was obtained as a single product in quantitative yield (entries 6 and 7).

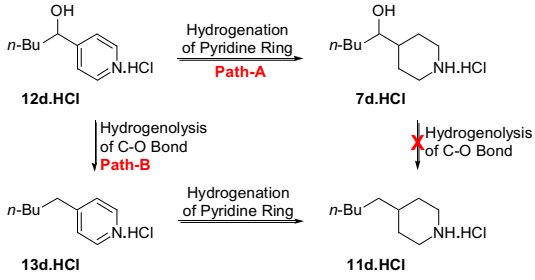
Table 3
Effect of structures of **6a–g** on the hydrogenation



Entry	**6**, **7**, **11** R=	Time (h)	**7·HCl/11·HCl**[a] (%)	Yield[b] (%)
1	(**a**) –H	12	65:35	99
2	(**b**) $-CH_3$	12	65:35	99
3	(**c**) $-C_2H_5$	8.5	75:25	99
4	(**d**) $-C_4H_9-n$	7.5	80:20	99
5	(**e**) $-C_5H_{11}-n$	7.0	93:07	99
6	(**f**) $-C_6H_{13}-n$	6.0	100:00	99
7	(**g**) $-C_8H_{17}-n$	5.5	100:00	99

[a] The ratio was measured by ^1H NMR.
[b] The isolated yields were obtained.

By carefully monitoring the hydrogenation of **6d** (entry 4, Table 3), we found that its pathway was similar to that of **5a**, and **12d·HCl** was a key intermediate (Scheme 6). Clearly, once **12d·HCl** was hydrogenated into **7d·HCl** by the path-A, **7d·HCl** will never be converted into **11d·HCl** because it is not a benzyl alcohol and its

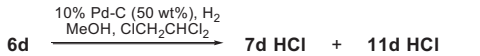


Scheme 6.

hydroxyl group could not be hydrogenolyzed under mild conditions.

As shown in Table 4, further experiments proved that the temperature had little influence on the selectivity between path-A and path-B (entries 1 and 2), but the pressure had significant influence (entries 3 and 4). When the hydrogenation of **6d** carried out at more than 40 psi (very low pressure, about 2.7 atm), **7d·HCl** was obtained as a single product in 99% yield. The early study results[8a] indicated that the formation of pyridine hydrochloride salt may change the adsorption nature of pyridine nucleus on the catalyst surface from edgewise to flat. Therefore, when the elevated hydrogen pressure was used in our experiments, their flatwise adsorption on the Pd–C catalyst surface could be increased and the hydrogenation was accelerated significantly.

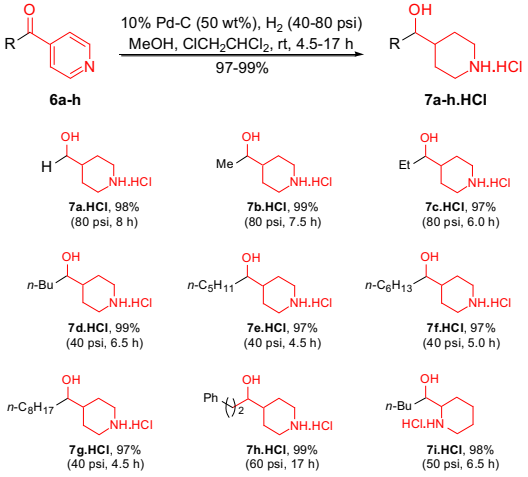
Table 4
Effects of the pressure and temperature on the hydrogenation of **6d**



Entry	Temp (°C)	Pressure (psi)	Time (h)	**7d·HCl**/**11d·HCl**[a] (%)	Yield[b] (%)
1	45	Balloon	6.5	80:20	99
2	55	Balloon	4.5	77:23	99
3	25	40	6.5	100:0	99
4	25	80	5.5	100:0	99

[a] The ratio was measured by ^{1}H NMR.
[b] The isolated yields were obtained.

As shown in Scheme 7, the different 4-alkanoylpyridines were selectively hydrogenated into the corresponding **7a**–**h**·**HCl** as single products in practical quantitative yields. When 2-alkanoylpyridine (**6i**) was used as a substrate, **7i**·**HCl** was obtained in similar excellent yields.



Scheme 7.

3. Conclusions

In conclusion, a novel Pd–C catalytic hydrodechlorination–hydrogenation was developed by a simple addition of 1 equiv of $ClCH_2CHCl_2$ into the conventional hydrogenation system. Under the selected temperature and pressure, the controlling transformations of 4-benzoylpyridines and 4-alkanoylpyridines were achieved to give the corresponding 4-benzylpiperidine hydrochlorides and α-alkyl-4-piperidinemethanol hydrochlorides. Since this multi-step one-pot reaction gave all products as crystalline salts, the work-up procedure was as simple as a filtration. The same excellent results were obtained when this method was performed at a 5-g scale.

4. Experimental section

4.1. General information and materials

The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$. TMS was used as an internal reference and *J* values are given in hertz.

4.2. A typical procedure for preparation of 4-substituted piperidine hydrochlorides

A suspension of **5a** (366 mg, 2.0 mmol), 10% Pd–C (183 mg, 50 wt %), and $ClCH_2CHCl_2$ (320 mg, 2.4 mmol) in MeOH (30 mL) was hydrogenated on an atmospheric pressure hydrogenator (or balloon) at 45 °C until the absorption of hydrogen ceased (4.5 h). After the Pd–C catalyst was filtered off, the solvent was removed on a rotavapor. The residue was diluted with diethyl ether (10 mL) to give the desired product **1a**·**HCl** (419 mg, 99%) as a white crystal. The product was collected simply by a filtration and usually was pure enough for any analytical purposes.

A similar procedure was used for the hydrogenation of **5b**–**i** to give the corresponding products **1b**–**i**·**HCl**.

*4.2.1. 4-Benzylpiperidine hydrochloride (**1a**·**HCl**).* White crystal, mp 180–181 °C (MeOH–Et_2O) (lit.[13a] 177–179 °C). ^{1}H NMR δ 7.33–7.25 (m, 2H), 7.23–7.15 (m, 3H), 3.35–3.25 (m, 2H), 2.86–2.77 (m, 2H), 2.53 (d, *J*=6.9 Hz, 2H), 1.85–1.70 (m, 3H), 1.44–1.25 (m, 2H); ^{13}C NMR δ 140.0, 129.4, 128.6, 126.4, 44.1, 41.5, 35.1, 28.2.

*4.2.2. 4-(4-Methylbenzyl)piperidine hydrochloride (**1b**·**HCl**).* White crystal, mp 218–220 °C (MeOH–Et_2O) (lit.[13b] 209–211 °C). ^{1}H NMR δ 7.12–7.05 (m, 4H), 3.35–3.25 (m, 2H), 2.87–2.77 (m, 2H), 2.48 (d, *J*=6.9 Hz, 2H), 2.20 (s, 3H), 1.81–1.72 (m, 3H), 1.39–1.24 (m, 2H); ^{13}C NMR δ 136.8, 135.5, 129.2, 129.0, 43.9, 41.2, 35.2, 28.2, 20.4.

*4.2.3. 4-(2-Methylbenzyl)piperidine hydrochloride (**1c**·**HCl**).* White crystal, mp 205–207 °C (MeOH–Et_2O) (lit.[6b] 202–204 °C). ^{1}H NMR δ 7.17–7.05 (m, 4H), 2.33–3.23 (m, 2H), 2.82–2.72 (m, 2H), 2.49 (d, *J*=6.87 Hz, 2H), 2.19 (s, 3H), 1.77–1.68 (m, 3H), 1.44–1.26 (m, 2H); ^{13}C NMR δ 138.2, 136.9, 130.4, 130.3, 126.6, 125.9, 44.1, 38.7, 34.0, 28.3, 18.6.

*4.2.4. 4-(2-Methoxylbenzyl)piperidine hydrochloride (**1d**·**HCl**).* White crystal, mp 172–174 °C (MeOH–Et_2O) (lit.[4f] 175–177 °C). ^{1}H NMR δ 7.07 (d, *J*=8.2 Hz, 2H), 6.83 (d, *J*=8.6 Hz, 2H), 3.69 (s, 3H), 3.33–3.23 (m, 2H), 2.83–2.73 (m, 2H), 2.49 (d, *J*=6.5 Hz, 2H), 1.77–1.65 (m, 3H), 1.37–1.20 (m, 2H); ^{13}C NMR δ 157.2, 132.6, 130.4, 113.9, 55.4, 44.0, 40.5, 35.2, 28.1.

*4.2.5. 4-(3-Methoxylbenzyl)piperidine hydrochloride (**1e**·**HCl**).* White crystal, mp 150–152 °C (MeOH–Et_2O), (lit.[6b] 138–140 °C). ^{1}H NMR δ 7.21 (t, *J*=7.6 Hz, 1H), 6.81–6.70 (m, 3H), 3.72 (s, 3H), 3.33–3.23 (m, 2H), 2.87–2.76 (m, 2H), 2.49 (d, *J*=6.9 Hz, 2H), 1.80–1.69 (m, 3H), 1.42–1.24 (m, 2H); ^{13}C NMR δ 158.9, 141.8, 129.7, 122.2, 114.8, 111.7, 55.3, 44.0, 41.5, 35.0, 28.2.

*4.2.6. 4-(3,5-Dimethylbenzyl)piperidine hydrochloride (**1f**·**HCl**).* White crystal, mp 184–186 °C (MeOH–Et_2O). IR ν 3442, 2955, 1588 cm^{-1}; ^{1}H NMR δ 6.64–6.55 (m, 2H), 6.53–6.47 (m, 1H), 3.23–3.18 (m, 2H), 2.65–2.55 (m, 2H), 2.24 (d, *J*=5.8 Hz, 2H), 1.99 (s, 6H), 1.57–1.48 (m, 3H), 1.28–1.24 (m, 2H); ^{13}C NMR δ 139.8, 137.5, 127.4, 127.0, 43.9, 41.7, 35.2, 28.3, 20.8; MS *m*/*z* (%) 204 (11.7), 203 (M–HCl, 100.0), 202

(52.4). Calcd for $C_{14}H_{22}ClN$: C, 70.13; H, 9.25; N, 5.84; Found: C, 70.02; H, 9.28; N, 5.77.

*4.2.7. 4-(3,4-Dimethylbenzyl)piperidine hydrochloride (**1g·HCl**).* White crystal, mp 218–219 °C (MeOH–Et_2O); IR ν 3420, 2909, 1586 cm^{-1}; ^1H NMR δ 6.77–6.73 (m, 2H), 6.69–6.66 (m, 1H), 3.26–3.21 (m, 2H), 2.69–2.60 (m, 2H), 2.26 (d, J=6.54 Hz, 2H), 1.94 (s, 3H), 1.91 (s, 3H); 1.59–1.50 (m, 3H), 1.34–1.25 (m, 2H); ^{13}C NMR δ 137.3, 136.2, 133.7, 130.4, 129.5, 126.7, 43.9, 41.3, 35.3, 28.3, 19.1, 18.7; MS m/z (%) 204 (11.1), 203 (M–HCl, 100.0), 202 (44.8). Calcd for $C_{14}H_{22}ClN$: C, 70.13; H, 9.25; N, 5.84; Found: C, 69.93; H, 9.18; N, 5.96.

*4.2.8. 4-(2,4-Dimethoxylbenzyl)piperidine hydrochloride (**1h·HCl**).* White crystal, mp 178–180 °C (MeOH–Et_2O). IR ν 3449, 2932, 1611, 1506 cm^{-1}; ^1H NMR δ 6.83–6.80 (m, 1H), 6.36–6.28 (m, 2H), 3.61 (s, 3H), 3.60 (s, 3H), 3.28–3.22 (m, 2H), 2.75–2.56 (m, 2H), 2.28 (d, J=6.5 Hz, 2H), 1.63–1.58 (m, 3H), 1.33–1.24 (m, 2H); ^{13}C NMR δ 158.8, 158.2, 131.4, 120.4, 104.8, 98.6, 55.44, 55.36, 44.0, 35.2, 33.9, 28.3; MS m/z (%) 235 (M–HCl, 31.2), 151 (100.0). Calcd for $C_{14}H_{22}ClNO_2$: C, 61.87; H, 8.16; N, 5.15; Found: C, 61.68; H, 8.18; N, 5.21.

*4.2.9. α-(4-Fluorophenyl)-4-piperidinemethanol hydrochloride (**1i·HCl**).* White crystal, mp 248–250 °C (dec, MeOH–Et_2O). IR ν 3339, 2950, 2813, 2718, 1509 cm^{-1}; ^1H NMR δ 7.32–7.28 (m, 2H), 7.12–7.03 (m, 2H), 4.40 (d, J=8.2 Hz, 1H), 3.47–3.42 (m, 1H), 3.35–3.25 (m, 1H), 2.96–2.75 (m, 2H), 2.08–2.15 (m, 1H), 1.97–1.85 (m, 1H), 1.55–1.28 (m, 3H); ^{13}C NMR δ 163.8, 160.6, 137.5, 128.7, 128.5, 115.5, 115.2, 76.6, 43.9, 43.8, 40.1, 25.1, 25.0; MS m/z (%) 209 (M–HCl, 32), 30 (100.0); Calcd for $C_{12}H_{17}ClFNO$: C, 58.66; H, 6.97; N, 5.70; Found: C, 58.67; H, 7.12; N, 5.55.

4.3. A typical procedure for preparation of α-substituted-4-pyridinemethanol hydrochlorides

The suspension of **6d** (326 mg, 2.0 mmol), 10% Pd–C (163 mg, 50 wt %), and $ClCH_2CHCl_2$ (320 mg, 2.4 mmol) in MeOH (30 mL) was hydrogenated on a Parr-Hydrogenator (40 psi, about 2.7 atm) at room temperature until the absorption of hydrogen ceased (4.2 h). After the Pd–C catalyst was filtered off, the solvent was removed on a rotavapor. The residue was diluted with diethyl ether (10 mL) to give the desired product **7d·HCl** (410 mg, 99%) as a white crystal. The product was collected simply by a filtration and usually was pure enough for any analytical purposes.

A similar procedure was used for the hydrogenation of **6a–c** and **6e–i** to give the corresponding products **7a–c·HCl** and **7e–i·HCl**.

*4.3.1. 4-Pyridinemethanol hydrochloride (**7a·HCl**).* White crystal, mp 128–130 °C (MeOH–Et_2O). IR ν 3261, 2937, 2888, 2821, 2731, 2509 cm^{-1}; ^1H NMR δ 3.40 (t, J=10.7 Hz, 4H), 2.93 (t, J=12.4 Hz, 2H), 1.88 (d, J=14.1 Hz, 2H), 1.81–1.68 (m, 1H), 1.25–1.42 (m, 2H); ^{13}C NMR δ 65.5, 43.8, 35.4, 25.1; MS m/z (%) 117 (18.5), 116 (56.1), 115 (M–HCl, 43.1), 30 (100.0). Calcd for $C_6H_{14}ClNO$: C, 47.52; H, 9.31; N, 9.24; Found: C, 47.17; H, 9.41; N, 9.11.

*4.3.2. α-Methyl-4-pyridinemethanol hydrochloride (**7b·HCl**).* White crystal, mp 108–110 °C (MeOH–Et_2O). IR ν 3404, 2968, 2812, 2722, 2496, 1602 cm^{-1}; ^1H NMR δ 3.58–3.42 (m, 1H), 3.42–3.30 (m, 2H), 2.83–3.01 (m, 2H), 2.02–1.95 (m, 1H), 1.84–1.79 (m, 1H), 1.62–1.52 (m, 1H), 1.50–1.35 (m, 2H), 1.15–1.05 (m, 3H); ^1H NMR (CD_3OH) δ 3.55–3.50 (m, 1H), 3.42–3.35 (m, 2H), 2.98–2.85 (m, 2H), 2.07–2.00 (m, 1H), 1.84–1.78 (m, 1H), 1.55–1.43 (m, 3H), 1.14 (d, J=6.2 Hz, 3H); ^{13}C NMR δ 70.4, 44.1, 44.0, 40.2, 28.2, 24.6, 24.3, 19.1; MS m/z (%) 130 (1.8), 129 (M–HCl, 17.1), 30 (100.0). Calcd for $C_7H_{16}ClNO$: C, 50.75; H, 9.73; N, 8.46; Found: C, 50.66; H, 9.85; N, 8.44.

*4.3.3. α-Ethyl-4-pyridinemethanol hydrochloride (**7c·HCl**).* White crystal, mp 106–108 °C (MeOH–Et_2O). IR ν 3394, 3068, 2959, 1578 cm^{-1}; ^1H NMR δ 2.42–2.29 (m, 3H), 2.95–2.83 (m, 2H), 1.97–1.89 (m, 1H), 1.82–1.73 (m, 1H), 1.71–1.57 (m, 1H), 1.53–1.30 (m, 4H), 0.83 (t, J=7.2 Hz, 3H); ^{13}C NMR δ 75.6, 44.2, 44.1, 38.3, 25.8, 25.1, 23.8, 9.4; MS m/z (%) 143 (M–HCl, 75.1), 84 (100.0). Calcd for $C_8H_{18}ClNO$: C, 53.47; H, 10.10; N, 7.80; Found: C, 53.52; H, 10.14; N, 7.78.

*4.3.4. α-Butyl-4-pyridinemethanol hydrochloride (**7d·HCl**).* White crystal, mp 112–114 °C (MeOH–Et_2O). IR ν 3392, 2954, 1579 cm^{-1}; ^1H NMR δ 3.46–3.43 (m, 3H), 3.02–2.91 (m, 2H), 2.05–1.95 (m, 1H), 1.89–1.81 (m, 1H), 1.76–1.62 (m, 1H), 1.59–1.25 (m, 8H), 1.91–1.82 (m, 3H); ^{13}C NMR δ 74.1, 44.3, 44.2, 38.9, 32.8, 27.5, 25.2, 23.8, 22.4, 138; MS m/z (%) 171 (M–HCl, 19.7), 82 (100.0). Calcd for $C_{10}H_{22}ClNO$: C, 57.82; H, 10.67; N, 6.74; Found: C, 57.75; H, 10.79; N, 6.72.

*4.3.5. α-Pentyl-4-pyridinemethanol hydrochloride (**7e·HCl**).* White crystal, mp 108–110 °C (MeOH–Et_2O); IR ν 3393, 3070, 2951, 1580 cm^{-1}; ^1H NMR δ 3.51–3.35 (m, 3H), 2.98–2.84 (m, 2H), 2.01–1.89 (m, 1H), 1.87–1.76 (m, 1H), 1.69–1.58 (m, 1H), 1.55–1.32 (m, 5H), 1.29–1.20 (m, 5H), 0.89–0.75 (m, 3H); ^{13}C NMR δ 74.0, 44.2, 44.1, 38.9, 33.1, 31.4, 25.2, 24.9, 23.7, 22.3, 13.7; MS m/z (%) 185 (M–HCl, 10.8), 84 (100.0). Calcd for $C_{11}H_{24}ClNO$: C, 59.57; H, 10.91; N, 6.32; Found: C, 59.68; H, 10.79; N, 6.47.

*4.3.6. α-Hexyl-4-pyridinemethanol hydrochloride (**7f·HCl**).* White crystal, mp 98–100 °C (MeOH–Et_2O); IR ν 3394, 3370, 3064, 2955 cm^{-1}; ^1H NMR δ 3.51–3.35 (m, 3H), 3.01–2.86 (m, 2H), 2.01–1.94 (m, 1H), 1.87–1.77 (m, 1H), 1.68–1.17 (m, 12H), 0.83 (t, J=6.00 Hz, 3H); ^{13}C NMR δ 74.0, 44.2, 38.9, 33.1, 31.4, 28.8, 25.2, 23.7, 22.3, 13.7; MS m/z (%) 199 (M–HCl, 5.5), 82 (100); Anal. Calcd for $C_{12}H_{26}ClNO$: C, 61.12; H, 11.11; N, 5.94. Found: C, 61.28; H, 11.07; N, 5.87.

*4.3.7. α-Octyl-4-pyridinemethanol hydrochloride (**7g·HCl**).* White crystal, mp 107–108 °C (MeOH–Et_2O). IR ν 3392, 3366, 3067, 2955 cm^{-1}; ^1H NMR δ 3.48–3.30 (m, 3H), 2.95–2.80 (m, 2H), 1.94–1.86 (m, 1H), 1.77–1.68 (m, 1H), 1.59–1.48 (m, 2H), 1.47–1.32 (m, 4H), 1.28–1.15 (m, 11H), 0.79 (t, J=5.8 Hz, 3H); ^{13}C NMR δ 73.9, 44.1, 44.0, 33.6, 31.9, 29.7, 29.4, 25.8, 25.4, 23.5, 22.6, 13.9; MS m/z (%) 227 (M–HCl, 7.9), 84 (100.0). Calcd for $C_{14}H_{30}ClNO$: C, 63.73; H, 11.46; N, 5.31; Found: C, 63.47; H, 11.32; N, 5.29.

*4.3.8. α-(2-Phenylethyl)-4-pyridinemethanol hydrochloride (**7h·HCl**).* White crystal, mp 170–171 °C (MeOH–Et_2O). IR ν 3628, 3382, 2947, 1578 cm^{-1}; ^1H NMR δ 7.29–7.11 (m, 5H), 3.42–3.29 (m, 3H), 2.89–2.66 (m, 3H), 2.59–2.46 (m, 1H), 1.91–1.82 (m, 1H), 1.72–1.56 (m, 3H), 1.51–1.35 (m, 3H); ^{13}C NMR δ 142.5, 128.7, 126.0, 73.2, 44.1, 44.0, 39.0, 35.3, 31.7, 25.2, 23.5; MS m/z (%) 219 (M–HCl, 2.7), 128 (100.0). Calcd for $C_{14}H_{22}ClNO$: C, 65.74; H, 8.67; N, 5.48; Found: C, 65.68; H, 8.44; N, 5.41.

*4.3.9. α-Butyl-2-pyridinemethanol hydrochloride (**7i·HCl**).* White crystal, mp 132–134 °C (MeOH–Et_2O); IR ν 3423, 2956, 2869, 1486 cm^{-1}; ^1H NMR δ 3.76–3.52 (m, 1H), 3.41–3.32 (m, 1H), 3.14–2.86 (m, 2H), 1.92–1.79 (m, 3H), 1.62–1.20 (m, 9H), 0.83 (s, 3H); ^{13}C NMR δ 71.4, 70.7, 61.3, 60.6, 45.1, 44.7, 32.0, 31.4, 27.4, 26.7, 25.3, 22.1, 21.9, 21.6, 21.4, 13.4; MS m/z (%) 171 (M–HCl, 0.05), 84

(100.0). Calcd for $C_{10}H_{22}ClNO$: C, 57.82; H, 10.67; N, 6.74; Found: C, 57.94; H, 10.48; N, 6.87.

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Supplementary data

These data include ^{1}H NMR and ^{13}C NMR spectra for all products **1a–i·HCl** and **7a–i·HCl** described in this article. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.12.017.

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