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A COMPARISON BETWEEN KBH_4 AND NaBH_4 IN THEIR REDUCTION OF PYRIDINIUM SALTS

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Abstract – This paper compares potassium borohydride and sodium borohydride in the reduction of pyridinium salts to tetrahydropyridines. The results indicate that potassium borohydride is more suitable for this reaction with low costs, mild reaction conditions and improved yields.

Tetrahydropyridines are an important category of heterocyclic compounds with various biological activities and medicinal value. They are widely found in natural products and synthetic drugs.¹⁻⁵ More importantly, tetrahydropyridines can be easily hydrogenated to afford piperidines, which are widely-used synthetic building blocks. Although various metal catalysts have been reported for the reduction of pyridines to piperidines,⁶⁻⁹ these catalysts are generally expensive and reaction conditions are also very harsh. Therefore, an indirect synthetic strategy from pyridinium salts is a good alternative (Figure 1). Since Panouse and Lyle reported the reduction of pyridinium salts with potassium borohydride and sodium borohydride,¹⁰ this methodology have been widely used and reported.¹¹

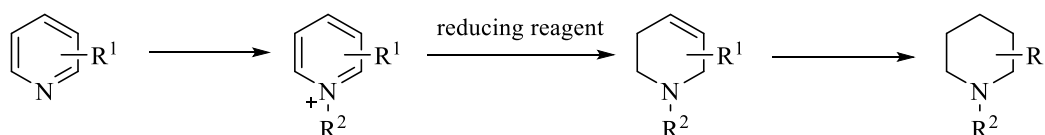


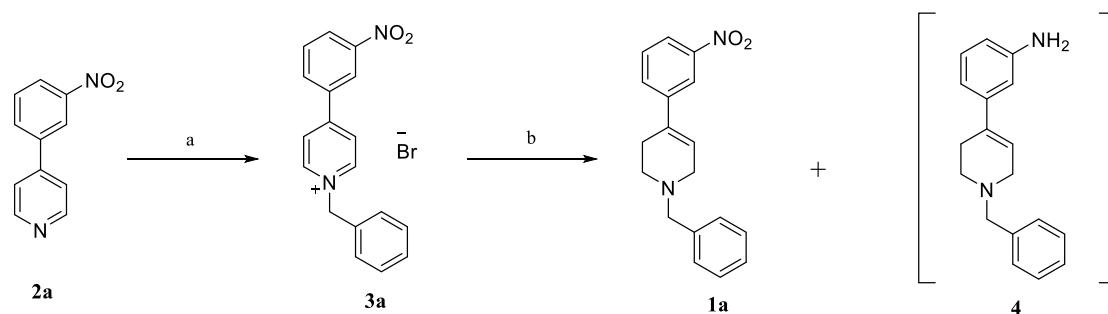
Figure 1. General synthetic route to piperidine derivative

Sodium borohydride was used in most cases as the reducing reagent to reduce pyridinium salts,¹²⁻¹⁴ while in a few reports potassium borohydride was used as the reducing reagent. In addition, the solvents were

either methanol or ethanol. Seemingly, these synthetic protocols were well-established, since the reported yields were generally very good and the reaction conditions were very mild.

Recently, we have to prepare 1-benzyl-4-(3-nitrophenyl)-1,2,3,6-tetrahydropyridine (**1a**) in multi-gram scale. When we first followed a common protocol (NaBH₄/MeOH), moderate yields were obtained. Thus, an optimization was then attempted. As a result, we found out a subtle distinction between sodium borohydride and potassium borohydride in this reduction, which has not yet been systematically revealed. Herein, we report the details of our investigation.

Our synthesis of 1-benzyl-4-(3-nitrophenyl)-1,2,3,6-tetrahydropyridine (**1a**) was shown in Scheme 1. The compound **2a**, prepared from pyridine-4-boronic acid,¹⁵ was treated with benzyl bromide to give the pyridinium salt **3a** in an 84% yield.¹⁶ Since sodium borohydride was most often used in this reduction, it was naturally first used as the reducing reagent.



Scheme 1. Reagents and conditions: (a) benzyl bromide (1.2 eq.), acetone, 60 °C, 84%; (b) KBH₄ (3.0 eq.), MeOH, -5 °C, 89%.

When the reaction was conducted at room temperature in methanol, a moderate yield was obtained (Table 1, entry 1). At room temperature, sodium borohydride in itself could react violently with methanol. In addition, a small amount of **4** was also produced as a major impurity. These results could be ascribed to the relatively high activity of sodium borohydride. When the temperature was lowered to -5 °C, the reaction of sodium borohydride with methanol could be effectively restrained and the yield of **1a** was increased to 71% (Table 1, entry 2). Nevertheless, we still hoped to further optimize the reaction conditions.

Therefore, NaBH(OAc)₃ was attempted as a reducing reagent. But its reducing activity was too low to effect this reduction (Table 1, entry 7). Finally, potassium borohydride was found out to be the best reducing reagent. It was slightly less active than NaBH₄. Potassium borohydride could reduce the

pyridinium salt **3a** smoothly, while it did not react violently with methanol in itself. The yield could be improved to 89%, when the reaction was conducted at $-5\text{ }^{\circ}\text{C}$ in methanol (Table 1, entry 5). Moreover, the results indicated that methanol and lower temperature was better than ethanol and higher temperature (Table 1, entries 4-6).

Table 1. The optimization of the reduction of **3a**

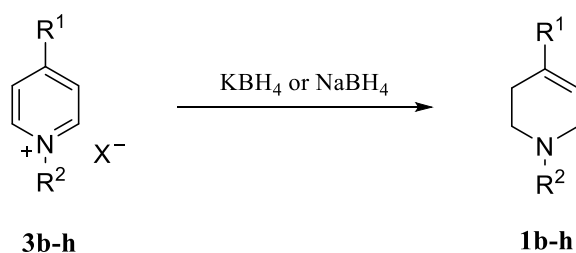
Entry	Reducing reagent	solvent	T ($^{\circ}\text{C}$)	T (h)	Yield ^a (%)
1	NaBH_4	MeOH	20	2.0	62
2	NaBH_4	MeOH	-5	4.5	71
3	NaBH_4	EtOH	-5	6.0	52
4	KBH_4	MeOH	20	2.0	78
5	KBH_4	MeOH	-5	4.5	89
6	KBH_4	EtOH	-5	5.0	63
7	$\text{NaBH}(\text{OAc})_3$	MeOH	-5	4.5	— ^b

[a] Isolated yield

[b] No products obtained

To explore the universality of the protocol, a series of pyridinium salts were prepared and subjected to the reduction with potassium borohydride and sodium borohydride, respectively. The results are summarized in Table 2. The detailed synthesis of these pyridinium salts can be seen in the supporting information. It can be seen that the yield of potassium borohydride was generally higher than that of sodium borohydride. This protocol was especially useful for those compounds bearing nitro- or cyano- groups, since more impurities might be produced, resulting in lower yields, when sodium borohydride was the reducing reagent.

Table 2. A comparison between KBH_4 and NaBH_4



Entry	R ¹	R ²	X	Product	Yield ^a (%)	Yield ^b (%)
1	H	benzyl	Br	1b	92	82
2	methyl	benzyl	Br	1c	90	80
3	methyl	4-nitrobenzyl	Br	1d	89	73
4	3-nitrophenyl	4-nitrobenzyl	Br	1e	84	63
5	4-cyanophenyl	benzyl	Br	1f	90	67
6	4-nitrophenyl	allyl	Br	1g	86	72
7	4-nitrophenyl	methyl	I	1h	87	77

[a] Isolated yield using KBH₄ as reducing reagent

[b] Isolated yield using NaBH₄ as reducing reagent

In conclusion, we studied the reduction conditions of pyridinium salts and compared potassium borohydride and sodium borohydride in this reaction. The potassium borohydride was preferable to sodium borohydride with better yields. This method was inexpensive, convenient and potential for industrial productions.

EXPERIMENTAL

Commercial reagents were used without further purification. Melting points were measured on a SGW X-4 (INESA) melting point apparatus and are uncorrected. ¹H NMR spectra were recorded on a Bruker DRX-500 (500 MHz) instrument. ¹³C NMR spectra were obtained on a JNMEX400 (125 MHz) instrument. Mass spectra (MS) were determined on a Bruker MicroTof II mass spectrometer or a Waters High Resolution UPLCTOFMS spectrometer. IR spectra were obtained using ATR on the FTIR Bruker Tensor 27.

General procedure for the reduction of pyridinium salts.

All reduction reactions were run on the multi-gram scale, using the following general procedure.

1-Benzyl-4-(3-nitrophenyl)-1,2,3,6-tetrahydropyridine (1a).¹⁷ To a solution of compound **3a** (1.0 g, 2.7 mmol) in MeOH (10 mL) at -5 °C was added KBH₄ (0.44 g, 8.1 mmol) slowly. The resulting mixture was stirred at -5 °C for 4.5 h. The reaction was quenched with acetaldehyde solution (40% aqueous solution, 2.7 g, 24.3 mmol). The mixture was then filtered and filtrate was evaporated to dryness. The residue was extracted with CH₂Cl₂ (3 × 10 mL) and washed with water (30 mL). The organic layer was

dried over anhydrous Na_2SO_4 , and concentrated. The crude product was purified by column chromatography on silica gel (petroleum ether : EtOAc, 5 : 1) to provide **1a** as a yellow solid (0.70 g, 89%). mp 51–53 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.26 (t, $J = 1.9$ Hz, 1H), 8.10 (dd, $J = 8.1, 1.5$ Hz, 1H), 7.72 (d, $J = 7.9$ Hz, 1H), 7.50 (t, $J = 8.0$ Hz, 1H), 7.42 – 7.36 (m, 4H), 7.32 – 7.28 (m, 1H), 6.26 – 6.24 (m, 1H), 3.69 (s, 2H), 3.25 – 3.23 (m, 2H), 2.79 (t, $J = 5.6$ Hz, 2H), 2.62 (br, 2H); LRMS (ESI) m/z (%): 295 (100) $[\text{M} + \text{H}]^+$.

1-Benzyl-1,2,3,6-tetrahydropyridine (1b).¹⁸ General procedure was followed, **3b** (4.0 mmol scale). The crude product was purified by column chromatography on silica gel (CH_2Cl_2) to provide **1b** as a liquid (0.64 g, 92%). ^1H NMR (500 MHz, CDCl_3) δ 7.29 – 7.23 (m, 4H), 7.19 – 7.16 (m, 1H), 5.70 – 5.66 (m, 1H), 5.61 – 5.57 (m, 1H), 3.51 (s, 2H), 2.91 – 2.89 (m, 2H), 2.49 (t, $J = 5.7$ Hz, 2H), 2.11 – 2.08 (m, 2H); LRMS (ESI) m/z (%): 174 (100) $[\text{M} + \text{H}]^+$.

1-Benzyl-4-methyl-1,2,3,6-tetrahydropyridine (1c).⁶ General procedure was followed, **3c** (7.6 mmol scale). The crude product was purified by column chromatography on silica gel (CH_2Cl_2) to provide **1c** as a liquid (1.28 g, 90%). ^1H NMR (500 MHz, CDCl_3) δ 7.39 – 7.32 (m, 4H), 7.29 – 7.26 (m, 1H), 5.40 – 5.38 (m, 1H), 3.60 (s, 2H), 2.97 – 2.96 (m, 2H), 2.58 (t, $J = 5.8$ Hz, 2H), 2.10 (br, 2H), 1.70 (br, 3H); LRMS (ESI) m/z (%): 188 (100) $[\text{M} + \text{H}]^+$.

1-(4-Nitrobenzyl)-4-methyl-1,2,3,6-tetrahydropyridine (1d). General procedure was followed, **3d** (3.9 mmol scale). The crude product was purified by column chromatography on silica gel (CH_2Cl_2) to provide **1d** as a yellow solid (0.80 g, 89%). mp 72–74 °C; ^1H NMR (500 MHz, CDCl_3) δ 8.17 (d, $J = 8.7$ Hz, 2H), 7.53 (d, $J = 8.6$ Hz, 2H), 5.37 – 5.35 (m, 1H), 3.65 (s, 2H), 2.95 – 2.94 (m, 2H), 2.56 (t, $J = 5.8$ Hz, 2H), 2.08 (br, 2H), 1.69 (br, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 147.1, 146.6, 132.8, 129.5, 123.5, 118.9, 61.9, 52.9, 50.1, 30.7, 22.9; HRMS (ESI): m/z calcd. for $\text{C}_{13}\text{H}_{17}\text{N}_2\text{O}_2$ $[\text{M} + \text{H}]^+$: 233.1285; found: 233.1295; IR (ATR): 2795, 1511, 1343, 1112 cm^{-1} .

1-(4-Nitrobenzyl)-4-(3-nitrophenyl)-1,2,3,6-tetrahydropyridine (1e). General procedure was followed, **3e** (3.6 mmol scale). The crude product was purified by column chromatography on silica gel (petroleum ether : CH_2Cl_2 , 1 : 10) to provide **1e** as a yellow solid (1.02 g, 84%). mp 100–102 °C; ^1H NMR (500 MHz, CDCl_3) δ 8.23 – 8.18 (m, 3H), 8.09 – 8.07 (m, 1H), 7.70 (d, $J = 7.9$ Hz, 1H), 7.57 (d, $J = 8.6$ Hz, 2H), 7.48 (t, $J = 8.0$ Hz, 1H), 6.23 – 6.21 (m, 1H), 3.75 (s, 2H), 3.23 – 3.22 (m, 2H), 2.77 (t, $J = 5.6$ Hz, 2H), 2.61 (br, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 148.45, 147.27, 146.12, 142.18, 133.28, 130.74, 129.50, 129.26, 124.27, 123.63, 121.83, 119.69, 61.62, 53.14, 49.84, 27.85; HRMS (ESI): m/z calcd. for

$C_{18}H_{18}N_3O_4$ $[M + H]^+$: 340.1292; found: 340.1290; IR (ATR): 2813, 1511, 1343, 1112 cm^{-1} .

1-Benzyl-4-(4-cyanophenyl)-1,2,3,6-tetrahydropyridine (1f).¹⁹ General procedure was followed, **3f** (2.8 mmol scale). The crude product was purified by column chromatography on silica gel (petroleum ether : EtOAc, 1 : 1) to provide **1f** as a yellow solid (0.70 g, 90%). mp 85–87 °C. ¹H NMR (500 MHz, $CDCl_3$) δ 7.62 – 7.61 (m, 2H), 7.49 – 7.48 (m, 2H), 7.41 – 7.35 (m, 4H), 7.32 – 7.28 (m, 1H), 6.24 – 6.23 (m, 1H), 3.68 (s, 2H), 3.24 – 3.22 (m, 2H), 2.76 (t, $J = 5.7$ Hz, 2H), 2.58 (br, 2H); LRMS (ESI) m/z (%): 275 (100) $[M + H]^+$.

1-Allyl-4-(4-nitrophenyl)-1,2,3,6-tetrahydropyridine (1g). General procedure was followed, **3g** (3.1 mmol scale). The crude product was purified by column chromatography on silica gel (CH_2Cl_2 : EtOAc, 1:1) to provide **1g** as a yellow solid (0.65 g, 86%). mp 38–40 °C; ¹H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, $J = 8.6$ Hz, 2H), 7.51 (d, $J = 8.6$ Hz, 2H), 6.27 (br, 1H), 5.97 – 5.89 (m, 1H), 5.25 (d, $J = 17.1$ Hz, 1H), 5.20 (d, $J = 10.2$ Hz, 1H), 3.22 – 3.21 (m, 2H), 3.15 (d, $J = 6.5$ Hz, 2H), 2.74 (t, $J = 5.6$ Hz, 2H), 2.60 (br, 2H); ¹³C NMR (125 MHz, $CDCl_3$) δ 147.13, 146.64, 134.80, 133.67, 126.14, 125.44, 123.70, 118.31, 61.15, 53.05, 49.52, 27.86; HRMS (ESI): m/z calcd. for $C_{14}H_{17}N_2O_2$ $[M + H]^+$: 245.1285; found: 245.1294; IR (ATR): 2796, 1592, 1505, 1337, 1124 cm^{-1} .

1-Methyl-4-(4-nitrophenyl)-1,2,3,6-tetrahydropyridine (1h). General procedure was followed, **3h** (2.9 mmol scale). The crude product was purified by column chromatography on silica gel (petroleum ether : EtOAc, 1:1) to provide **1h** as a yellow solid (0.56 g, 87%). mp 107–109 °C; ¹H NMR (500 MHz, $CDCl_3$) δ 8.18 – 8.16 (m, 2H), 7.52 – 7.51 (m, 2H), 6.27 – 6.26 (m, 1H), 3.17 – 3.15 (m, 2H), 2.69 (t, $J = 5.7$ Hz, 2H), 2.61 – 2.59 (m, 2H), 2.42 (s, 3H); ¹³C NMR (125 MHz, $CDCl_3$) δ 147.16, 146.64, 133.32, 126.08, 125.44, 123.70, 54.95, 51.92, 45.59, 27.93; HRMS (ESI): m/z calcd. for $C_{12}H_{15}N_2O_2$ $[M + H]^+$: 219.1128; found: 219.1138; IR (ATR): 2782, 1586, 1498, 1330, 1093 cm^{-1} .

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