Supporting Information

A Strong Hydride Donating, Acid Stable and Reusable 1,4-Dihydropyridine for Selective Aldimine and Aldehyde Reductions

Yasukazu Hirao,* Hajime Eto, Mitsuru Teraoka and Takashi Kubo*
Department of Chemistry, Graduate School of Science, Osaka University, Toyonaka, Osaka 560-0043, Japan

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1. Synthesis

2,6-Dibromopyridine-N-oxide (3). To a solution of 2,6-dibromopyridine (9.07 g, 38.3 mmol) in TFA (50 mL) was added dropwise hydrogen peroxide (12 mL). The mixture was refluxed overnight under nitrogen atmosphere and quenched by water. The mixture was neutralized by NaHCO₃ aq. and extracted with dichloromethane. The organic layer was washed with brine and dried over anhydrous sodium sulfate. After filtration and concentration, the residue was purified by reprecipitation to give 3 as a pale-yellow solid (6.90 g, 71%); ¹H NMR (500 MHz, chloroform-d) δ (ppm) 7.65 (d, J = 8.0 Hz, 2H), 6.93 (t, J = 8.0 Hz, 1H); ¹³C NMR (126 MHz, chloroform-d) δ (ppm) 133.82, 129.57, 124.78; HRMS (ESI, positive): m/z Calcd for C₉H₅NBr₂O₇Na; 275.8453 [M+H]⁺; found: 275.8458.

2,6-Dibromo-4-nitropyridine-1-oxide (4) and 2,6-dibromo-4-nitropyridine (4'). To a solution of 3 (6.48 g, 25.6 mmol) in concentrated sulfuric acid (20 mL) at 0 °C was added dropwise fuming nitric acid (10 mL). The reaction mixture was heated at 90 °C overnight. The reaction solution was cooled down to room temperature and cautiously poured into crushed ice. The precipitate was filtered off, washed with water and dried under vacuum to afford 4 and 4’ as a light-yellow solid (6.49 g, 86%). 4,4’ = 7:1; ¹H NMR (500 MHz, chloroform-d) δ (ppm) 8.50 (s, 2H-4), 8.19 (s, 2H-4’); ¹³C NMR (126 MHz, chloroform-d) δ (ppm) 142.43, 140.17, 133.96, 123.52, 123.52, 120.56.

4-Amino-2,6-dibromopyridine (5). Iron powder (4.00 g, 69.2 mmol) was added to a suspension of 4 and 4’ (4.01 g, 13.4 mmol) in acetic acid (80 mL). After stirring at 100 °C for 90 minutes, the resulting mixture was cooled down, filtered through Celite, and neutralized with 6 M NaOH aq. The precipitate was filtered off with Celite and the filtrate was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. After filtration and concentration, the residue was purified by reprecipitation to give 5 as a pale-pink solid (3.03 g, 87%); ¹H NMR (500 MHz, chloroform-d) δ (ppm) 6.68 (s, 2H), 4.30 (s, 2H); ¹³C NMR (126 MHz, chloroform-d) δ (ppm) 155.38, 140.95, 111.99; HRMS (ESI, positive): m/z Calcd for C₉H₇NBr₂; 252.8794 [M+H]⁺; found: 252.8799.

4-Amino-2,6-dimesitylpyridine (6). Pyridyl bromide 5 (501 mg, 1.99 mmol), mesitylboronic acid (1.32 g, 8.05 mmol), tetrakis (triphenylphosphine) palladium (0) (345 mg, 0.299 mmol) and sodium carbonate (2.13 g, 20.1 mmol) were placed in a flask under nitrogen atmosphere. After adding toluene, ethanol and water (3:2:1, 18 mL) as solvent, the mixture was stirred at reflux overnight. After cooling and quenching the reaction with water, the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. After filtration and concentration, the residue was purified by column chromatography on alumina using a mixture of dichloromethane and hexane (1:4, v/v) as eluent and then recrystallized from hexane to afford 6 (566 mg, 79%) as a white solid; ¹H NMR (500 MHz, chloroform-d) δ (ppm) 6.86 (s, 4H), 6.42 (s, 2H), 4.14 (s, 2H), 2.27 (s, 6H), 2.08 (s, 12H); ¹³C NMR (126 MHz, chloroform-d) δ (ppm) 160.70, 153.24, 138.45, 136.88, 135.53, 127.94, 108.50, 21.06, 20.04; HRMS (ESI, positive): m/z Calcd for C₂₉H₂₇N₂; 331.2169 [M+H]⁺; found: 331.2177.

4-Bromo-2,6-dimesitylpyridine (7). To a suspension of 6 (108 mg, 0.303 mmol) and copper(II) bromide (144 mg, 0.645 mmol) in acetonitrile (5 mL) was added dropwise tert-butyl nitrite (0.3 mL) at 0 °C and stirred 30 minutes under nitrogen atmosphere. The mixture was allowed to warm to room temperature and then stirred for another 3 hours and quenched with 25% NH₃ aq. The mixture was extracted with dichloromethane. The organic layer was washed with brine and dried over anhydrous sodium sulfate. After filtration and concentration, the residue was purified by column chromatography on alumina using a mixture of dichloromethane and hexane (15:85, v/v) as eluent to afford 7 as a pale-yellow solid (119 mg, 82%); ¹H NMR (500 MHz, chloroform-d) δ (ppm) 7.38 (s, 2H), 6.90 (s, 4H), 2.29 (s, 6H), 2.05 (s, 12H); ¹³C NMR (126 MHz, chloroform-d) δ (ppm) 161.46, 137.74, 136.84, 135.44, 133.12, 128.23, 125.69, 21.08, 20.16; HRMS (ESI,
positive): m/z Calcd for C_{23}H_{24}NBr; 331.2169 [M+H]^+; found: 331.2177.

2,6-Dimesityl-4-phenylpyridine (8). Pyridyl bromide 7 (283 mg, 0.718 mmol), mesitylboronic acid (130 mg, 1.06 mmol), tetrakis (triphenylphosphine) palladium (0) (45 mg, 0.039 mmol) and sodium carbonate (241 mg, 2.27 mmol) were placed in a flask under nitrogen atmosphere. After adding toluene, ethanol and water (3:2:1, 18 mL) as solvent, the mixture was stirred at reflux overnight. The mixture was cooled down, quenched by water and extracted with dichloromethane. The organic layer was washed with brine and dried over anhydrous sodium sulfate. After filtration and concentration, the residue was purified by column chromatography on alumina using a mixture of dichloromethane and hexane (1:4, v/v) as eluent to afford 8 as a white solid (261 mg, 93%); ^1H NMR (500 MHz, chloroform-d) δ (ppm) 7.72–7.70 (m, 2H), 7.50–7.44 (m, 3H), 7.45 (s, 2H), 6.93 (s, 4H), 2.31 (s, 6H), 2.10 (s, 12H); ^13C NMR (126 MHz, chloroform-d) δ (ppm) 160.73, 148.78, 138.19, 138.11, 137.33, 135.65, 129.15, 129.12, 128.17, 127.02, 120.21, 21.10, 20.27; HRMS (ESI, positive): m/z Calcd for C_{29}H_{29}N; 392.2373 [M+H]^+; found: 392.2371.
Remarks on the assessment of the reduction reactions based on NMR spectroscopy.

To confirm the formation of alcohols in the reduction reactions, we used the spectra published in previous papers. The NMR spectra used to determine the yields are given at the end of the Supporting Information. Although the spectra of the entire solution after the reaction were presented, only peaks derived from compounds related to the reducing agent (1 and 2) and the reaction substrate (9 and 10) were observed, suggesting that the reduction reaction proceeded without side reactions. Note that during quenching process, HBF₃OH, a very strong Brønsted acid formed by the reaction of H₂O and BF₃, sometimes give a proton to the unreacted 1. This acid-base equilibrium broadens the NMR peaks of 1, making it difficult to analyze. However, acids had no effect on the reactant, product, or cation 2, and thus the reaction yield could be calculated accurately.

**N-Benzylaniline (10a).** H NMR (500 MHz, chloroform-d) δ (ppm) 7.38–7.32 (m, 5H), 7.28–7.25 (m, 1H), 7.16 (dd, 2H, J = 8.5, 7.5 Hz), 6.71 (tt, 1H, J = 7.5, 1.0 Hz), 6.64 (dd, 2H, J = 8.5, 1.0 Hz), 4.33 (s, 2H), 4.05 (bs, 1H).

**4-Methoxybenzyl alcohol (10c).** H NMR (500 MHz, chloroform-d) δ (ppm) 7.29 (d, 2H, J = 8.7 Hz), 6.89 (d, 2H, J = 8.7 Hz), 4.61 (s, 2H), 3.81 (s, 3H).

**4-Trifluoromethylbenzyl alcohol (10d).** H NMR (500 MHz, chloroform-d) δ (ppm) 7.60 (d, 2H, J = 8.3 Hz), 7.50 (d, 2H, J = 8.3 Hz), 4.95 (q, 1H, J = 6.5 Hz), 1.49 (d, 2H, J = 6.5 Hz).

**Cyclohexanemethanol (10e).** H NMR (500 MHz, chloroform-d) δ (ppm) 3.42 (d, 2H, J = 6.5 Hz), 2.0 (t, J = 11.4 Hz, 1 H), 1.75–1.65 (m, 5H), 1.50–1.43 (m, 1H), 1.28–1.11 (m, 3H), 0.99–0.88 (m, 2H).

**1-Phenylethanol (10g).** H NMR (500 MHz, chloroform-d) δ (ppm) 7.39–7.33 (m, 5H), 4.90 (q, 1H, J = 6.2 Hz), 1.50 (d, 2H, J = 6.2 Hz).

**1-(4-Methoxyphenyl)ethanol (10h).** H NMR (500 MHz, chloroform-d) δ (ppm) 7.30 (d, 2H, J = 8.8 Hz), 6.87 (d, 2H, J = 8.8 Hz), 4.84 (q, 1H, J = 6.5 Hz), 1.47 (d, 2H, J = 6.5 Hz).

**1-(4-Trifluoromethyl)phenylethanol (10i).** H NMR (500 MHz, chloroform-d) δ (ppm) 7.60 (d, 2H, J = 8.3 Hz), 7.50 (d, 2H, J = 8.3 Hz), 4.95 (q, 1H, J = 6.5 Hz), 1.49 (d, 2H, J = 6.5 Hz).

**Cyclohexanone (10n).** H NMR (500 MHz, chloroform-d) δ (ppm) 2.34 (t, J = 5.0 Hz, 4H), 1.89–1.84 (m, 4H), 1.75–1.71 (m, 2H).

These peaks overlap with peaks derived from other compounds (1, 9, or diethyl ether). Therefore, the values of the peaks shown here are those of the cited literatures. The reaction yields were calculated using the other peaks.
2. Electrochemical measurements

As an example of conventional dihydropyridines, the redox behavior of BNAH and its oxidized form, BNA⁺, was investigated electrochemically. The reduction corresponding to the Py⁺/• process was observed as an irreversible process, very different from that of 2 (Fig. S1a and b). The peak corresponding to the re-oxidation was observed around −0.5 V, suggesting that a chemical reaction occurred after the reduction process. In addition, the reverse current as an indicator of reversibility was almost not observed in this process even in the fast scan using the OSWV method. Furthermore, no reduction corresponding to the Py⁻⁻ process was observed. The significant difference in the reversibility of the redox processes of pyridinium proves that the introduction of bulky substituents in 2 enables stable electron transfer. The oxidation process of BNAH is shown in Fig. S1c and d. Since the oxidation process of dihydropyridine is an irreversible process involving chemical reactions, the observed behavior was not different from that of 1. The electron-withdrawing group in BNAH shifted the oxidation peak to a higher potential.

![CV and OSWV for (a, b) the reduction of BNA⁺ and (c, d) the oxidation of BNAH. Voltammograms were taken at scan rates of 100 mV s⁻¹ (CV) and 600 mV s⁻¹ (scan frequency 150 Hz and step voltage 4 mV) (OSWV) in acetonitrile containing 0.1 M n-Bu₄NPF₆ as supporting electrolyte.](image-url)
3. Isothermal titration calorimetry (ITC)

**Fig. S2** ITC for a) the hydride transfer from BNAH to 9-phenylxanthylum perchlorate ($\text{Xan}^+\text{ClO}_4^-$) in acetonitrile at 298 K and b) the hydride transfer from Hantzsch ester (HEH) to $\text{Xan}^+\text{ClO}_4^-$ in acetonitrile at 298 K.

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**Note:** The diagrams depict the chemical reactions and the corresponding power changes over time in an ITC experiment.
4. NMR spectra
$\text{Mes} - \text{Mes}$

1) 1.2 eq BF$_3$·OEt$_2$

diethyl ether, 30°C, 2 h

2) 2.0 eq H$_2$O

diethyl ether

$\text{Mes} - \text{Mes}$
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References