A Mild Procedure for the Reduction of Pyridine *N*-Oxides to Piperidines Using Ammonium Formate

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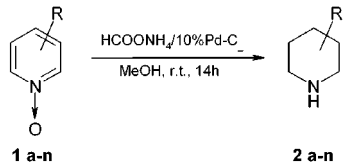
Substituted piperidines can be prepared using a variety of methods.[1] The simplest procedure is by reduction of the corresponding pyridines. This process has generally required the use of high pressures and temperatures.[2] Mild conditions for the reduction of a variety of pyridines, quinolines, and isoquinolines was achieved by using a metal alloy.[3] This method is not selective, and many functional groups are reduced under these conditions. For example, the reduction of 2-phenylpyridine with nickel−aluminum alloy in dilute base gives 2-cyclohexylpiperidine. Similarly, pyridines are reduced to piperidine with a lanthanoid metal−hydrochloric acid system.[4] This procedure is limited by the choice of the Ln metal, leads to a mixture of unsaturated piperidines, and does not always proceed in good yield. Also, reduction of pyridine-containing heterocycles with lithium triethylborohydride (super-hydride) has been reported in the literature.[5] Again, this method is limited by the substituents on the ring. For example, 3,4-lutidine is reduced to a mixture of tetrahydropyridines and both 2,6-lutidine and 2-(3-pentenyl)pyridine are totally inert to these conditions. In this paper, we wish to report a mild procedure for the reduction of pyridine or substituted pyridine *N*-oxides to piperidines. This is accomplished by catalytic transfer hydrogenation with ammonium formate as the hydrogen source, in the presence of palladium on carbon.

A number of methods have been described for the reduction of heteroaromatic *N*-oxides to the corresponding aromatic derivatives.[6] These procedures are efficient for the reduction of *N*-oxide and not the aromatic ring. Our goal, therefore, was to develop a general and mild procedure for the reduction of pyridine *N*-oxides[7] (Scheme 1). It was observed that ammonium formate/palladium on carbon is a convenient system for this reduction. The reaction is carried out in methanolic solution overnight at room temperature. The procedure is simple and does not require special apparatus, hydrogen atmosphere, or harsh conditions. The workup is easy, requiring only filtration of catalyst followed by removal of the solvent. Other reducing systems appear to be inefficient under this type of reduction conditions, for example, ammonium formate/Rh on carbon, hydrogen/Pd on carbon, or tin hydride.

Scheme 1



1 a-n **2 a-n**

Our results are summarized in Table 1. A variety of pyridines, quinolines (entry 1m), and isoquinolines (entry 1n) are converted efficiently to their piperidine derivatives. The method is general, and several reducible functionalities such as methoxycarbonyl (entry 1f), carboxyl (entry 1g), amino (entries 1h−j), hydroxy (entry 1e), and amide (entries 1k,l) are unaffected with this reagent system. However, the chlorine atom in the 2 position is readily eliminated under the standard reaction conditions. In the case of 4-cyano, deoxygenation of the *N*-oxide and the reduction of the cyano function to the corresponding alkylamine[9b] are the only products observed in the reaction mixture. In the reaction of 2-carboxylpyridine *N*-oxide with ammonium formate, low yield of the reduction product was observed by ^{1}H NMR. In contrast, the corresponding 2-methyl ester pyridine *N*-oxide gave a high yield of the expected reduced compound. We hypothesized that a strong hydrogen bond is formed between the hydrogen of the carboxyl group and the oxygen of the N−O. This leads to the deactivation of the pyridine ring toward the reduction. However, in the case of the ester, this bond no longer exists and the reduction readily occurs using this procedure. Heating the reaction also affects the yield. For example, reduction of 2-hydroxypyridine *N*-oxide (entry 1e) in methanol at room temperature overnight gave only 50% yield of the expected product. The yield increases to 98% when the reaction was carried under reflux.

In conclusion, we developed an efficient procedure for the reduction of pyridine *N*-oxide to piperidine using ammonium formate[9]−palladium on carbon. The advantages of this procedure are as follows: simplicity of the reaction, high yield, mild conditions, and the avoidance of strong acid and harsh reagents. This approach is expected to be applicable to synthesize stereoselective piperidines using chiral catalyst. Investigations toward the preparation of such compounds are in progress.

Experimental Section

Melting points were measured on an Electrothermal melting point apparatus and are uncorrected.^{1}H NMR spectra were obtained on a Brucker DRX-400 or on a Varian Inova 400 spectrometer. Mass spectra were recorded on a Micromass

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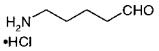
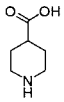
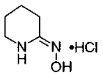
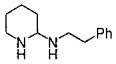
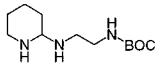
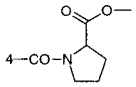
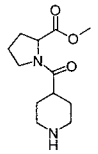
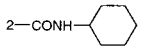
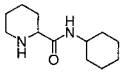
Table 1. Reduction of *N*-Oxides with Ammonium Formate

Substrate[a]	R	Product[b]	Yield (%)
1a	H		95[c]
1b	3-CH_3		100[d]
1c	4-CH_3		84[d]
1d	2-Cl		100[d]
1e	2-OH		98[d,e]
1f	2-$COOCH_3$		84[d]
1g	4-COOH		99[d]
1h	2-NH_2		43[d]
1i	2-$NH(CH_2)_2Ph$		90[d]
1j	2-$NH(CH_2)_2NHBOC$		85[d]
1k			84[c]
1l			90[c]
1m	quinoline N-oxide		87[d]
1n	isoquinoline N-oxide		84[d]

[a] *N*-Oxides are commercially available or are simply prepared by the oxidation of the corresponding pyridines with *m*-CPBA.[6] [b] All products had spectroscopic characteristics consistent with the assigned structures. [c] Based on ^{1}H NMR spectrum. [d] Isolated yield. [e] The reaction is heated overnight in methanol under reflux.

Platform LCZ instrument. Ammonium formate was obtained from Aldrich (Milwaukee, WI), and all pyridine *N*-oxides were obtained from either Aldrich (Milwaukee, WI) or TCI America (Portland, OR).

Typical Procedure for the Preparation of Piperidine (1b). Dry ammonium formate (1.2 g, 18 mmol) was added to a solution of 3-picoline *N*-oxide (200 mg, 1.83 mmol) containing palladium on carbon 10% (195 mg) in anhydrous methanol (18 mL) under an atmosphere of nitrogen. The reaction was allowed to stir for 16 h at room temperature, and the solution was filtered. The filtrate was treated with a 10% HCl solution in methanol (5 mL), and the solvent was evaporated under reduced pressure. The piperidine hydrochloride **1b** (249 mg, 100%) was isolated without further purification as a white solid. Mp: 173 °C; ^{1}H NMR (400 MHz, D_2O): δ 0.79 (d, J = 6 Hz, 3H, CH_3); 1.03 (m, 1H, CH); 1.53 (m, 1H, $CHCH_2CH_2$); 1.69 (m, 3H, $CHCH_2CH_2$); 2.44 (t, J = 12 Hz, 1H, CH_2CH_2NH); 2.71 (td, J = 3, 12 Hz, 1H, CH_2CH_2NH); 3.14 (m, 2H, $CHCH_2NH$). LRMS (ESI) m/z 100 (MH^+).

Registry numbers (supplied by author): piperidine hydrochloride, 6091-44-7; 3-pipecoline hydrochloride, 58531-29-6; 4-pipecoline hydrochloride, 42796-28-1; 2-hydroxypiperidine hydrochloride, 100707-36-6; 5-aminopentanal, 14049-15-1; picolinic acid methyl ester *N*-oxide, 38195-81-2; methyl pipecolinate hydrochloride, 35559-18-5; 4-piperidine carboxylic acid, 498-94-2; 2-piperidinamine, 45505-62-2; piperidin-2-one oxime hydrochloride, 14299-97-9; [2-[(1-oxido-2-pyridinyl)amino]-carbamic acid 1,1-dimethylethyl ester, 187339-12-4; 1,2,3,4-tetrahydroquinoline, 635-46-1; 1,2,3,4-tetrahydroisoquinoline, 91-21-4.

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