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The mechanism of unexpected reduction of dimethyl pyridine-2,3-dicarboxylate to 1,2,3,4-tetrahydrofuro[3,4-*b*] pyridin-5(7*H*)-one with sodium borohydride

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Abstract

An unexpected reduction of dimethyl pyridine-2,3-dicarboxylate to 1,2,3,4-tetrahydrofuro[3,4-*b*]pyridin-5(7*H*)-one with sodium borohydride in ethanol and tetrahydrofuran, respectively, is described, a hypothetic mechanism for the unusual reductive product is proposed.

Keywords: Reduction; Sodium borohydride; Dimethyl pyridine-2,3-dicarboxylate; 1,2,3,4-Tetrahydrofuro[3,4-*b*]pyridin-5(7*H*)-one; Reaction mechanism

As a mild and efficient reducing agent, sodium borohydride ($NaBH_4$) has been applied to a wide range of reduction processes, such as aldehydes and ketones to alcohols, imines to amines [1]. In some cases, it can also reduce carboxylic esters to alcohols in the presence of certain additives, such as iodine [2], zinc chloride [3], and so on, which can enhance the reactivity of $NaBH_4$. Boechat and coworkers found that aromatic esters [4] and heteroaromatic esters [5] could be transformed into the corresponding alcohols by the addition of methanol to $NaBH_4$ in tetrahydrofuran (THF). Another example for the reduction of heteroaromatic ester with $NaBH_4$ reported by Yoshiizumi *et al.* [6], who claimed the reaction between dimethyl pyridine-2,3-dicarboxylate and $NaBH_4$ in ethanol resulted in corresponding diol **2** in 85% yield (Scheme 1).

The aforementioned reaction was employed in our lab most recently under the same conditions as reported previously [6]. Surprisingly, besides compound **2**, a minor amount of unexpected tetrahydropyridine derivative **3** was also observed (Scheme 1). Moreover, when we conducted the reaction in THF instead of ethanol, compound **3** was obtained as the only product. Because the reduction of pyridyl ring with $NaBH_4$ is so unusual, the formation of compound **3** from **1** is much interesting. Here we will discuss the probable mechanism of the very unexpected reduction.

Similar to the $NaBH_4$–MeOH system reported by Boechat *et al.* [4,5], the reductive potency of $NaBH_4$ towards esters could be enhanced in the presence of ethanol, therefore treatment of compound **1** with $NaBH_4$ in ethanol

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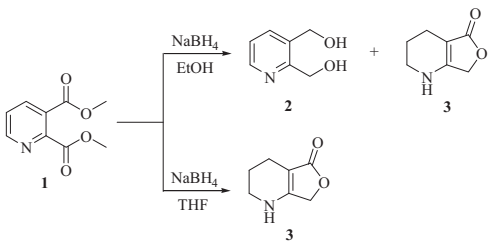
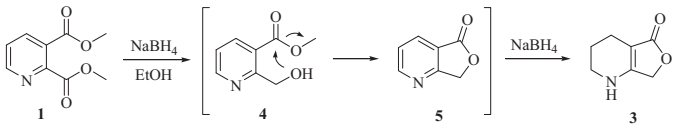


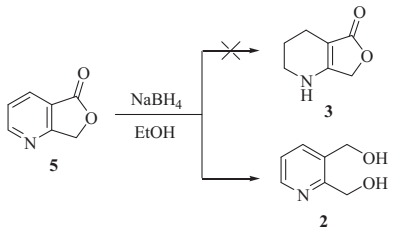
Scheme 1.



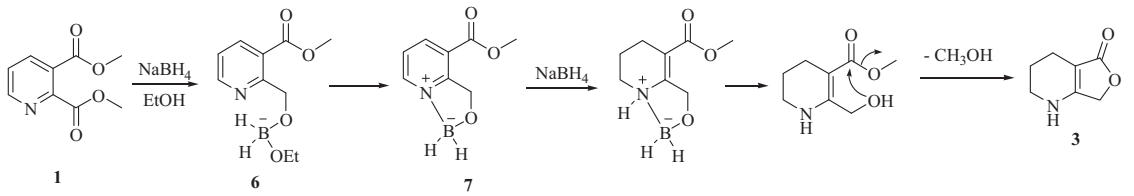
Scheme 2.

afforded diol **2** as major product. We initially considered minor product **3** was probably achieved through the pathway as shown in Scheme 2. That was, reduction of 2-ester group (more electron-deficient and therefore to be reduced much easier than 3-ester group due to nitrogen's inductive effect) followed by intramolecular transesterification to convert compound **1** into lactone **5**, which was then reduced to **3**. To investigate this putative pathway, reaction between compound **5** and $NaBH_4$ was carried out in ethanol. However, there was no compound **3** observed and compound **2** was obtained as the only product (Scheme 3). The results above suggested that **3** should be achieved through other reaction mechanism.

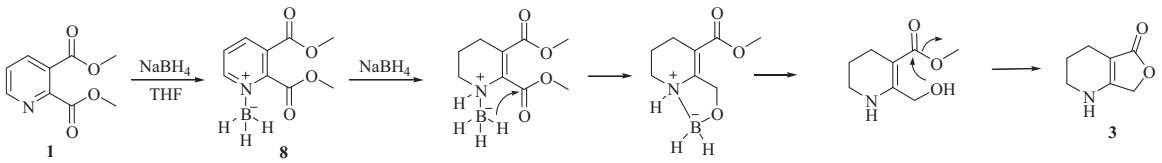
Despite the rarity of reducing pyridines into tetrahydropyridines with $NaBH_4$, there were also some reports on tetrahydropyridines reduced from pyridinium salts [7–11], which usually produced from pyridines. It is well known that pyridinium salts are much easier to be reduced with $NaBH_4$ because of its pyridyl ring's lower electron cloud density than pyridines'. Additionally, Brossi and coworkers had reported amine-borane complexes were achieved by the reaction between pyridinium salts and $NaBH_4$ [12]. From above it could be assumed that the unusual reduction in this research was probably performed through nitrogen–boron complex intermediate pathway. Scheme 4 described the possible mechanism for the formation of **3** in ethanol briefly. 2-Ester group of compound **1** was reduced firstly and intermediate **6** was given, thereafter nitrogen coordinated with boron to form nitrogen–boron complex **7**, whose



Scheme 3.



Scheme 4.



Scheme 5.

pyridyl ring (with lower electron cloud density than compound **1**) was reduced and intramolecular transesterification was proceeded subsequently to yield compound **3**.

When THF instead of ethanol was used as solvent, the reductive activity of $NaBH_4$ towards ester would be decreased, so it is difficult to reduce 2,3-biester moiety of compound **1** immediately. Instead, the pyridine-borane complex **8** was formed first as shown in Scheme 5. Due to the presence of two electron-withdrawing ester groups and the pyridine-borane complex, the electron cloud density of the pyridyl ring was low enough to allow its direct reduction to the tetrahydropyridine ring. Subsequent reduction of 2-ester group and intramolecular transesterification provided compound **3** finally. Notably, the reaction needed to be performed at high temperature (heating to vigorous reflux and even over 75 °C) [13], otherwise neither pyridyl ring nor ester moiety of compound **1** could be reduced.

To summarize, it is so unusual to reduce pyridines with $NaBH_4$ and the unexpected and interesting results in this study add some valuable information on the reduction of this kind of compounds under mild reaction conditions. Further studies on the reduction of pyridines with diverse substituents as well as other nitrogen-containing heteroaromatic compounds with $NaBH_4$ are in process.

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[13] Reduction of dimethyl pyridine-2,3-dicarboxylate with $NaBH_4$. Entry 1: To a solution of dimethyl pyridine-2,3-dicarboxylate (195 mg, 1 mmol) in 5 mL ethanol was added $NaBH_4$ (190 mg, 5 mmol) at 0 °C. The reaction mixture was refluxed for 20 h and then filtered while the solution is hot. The filter cake was washed with hot ethanol and the combined filtrate was then concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2:CH_3OH:Et_3N = 15:5:1) to give 83 mg compound **2** (yield 60%) and 15 mg compound **3** (yield 11%). Entry 2: Dimethyl pyridine-2,3-dicarboxylate (195 mg, 1 mmol) was resolved in 5 mL THF, to the mixture was added $NaBH_4$ (190 mg, 5 mmol) at 0 °C. The reaction mixture was heated to vigorous reflux for 4 h and then cooled to rt. 2 mL H_2O was added to the mixture, which allowed stirring for another 10 min. To the mixture was then added 5 mL $CHCl_3$ and the organic phase was separated. After extracting the water phase with $CHCl_3$ (5 mL ×2), the combined organic phase were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (CH_2Cl_2:CH_3OH:Et_3N = 15:5:1) to give 103 mg compound **3** (yield 74%). **3**: slight yellow solid, mp 129–131 °C; ^{1}H NMR (300 MHz, acetone-d_6): δ 6.42 (br, 1H), 4.54 (s, 2H), 3.31 (m, 2H), 2.13 (t, 2H, J = 6.0 Hz), 1.78 (m, 2H); ^{13}C NMR (75 MHz, acetone-d_6): δ 173.9, 164.5, 90.8, 66.2, 41.8, 21.7, 18.3; HR-FAB-MS: m/z 140.0705 $[M+H]^+$ (calcd. for $C_{10}H_{15}O_5$: 140.0712).