# Silane Reduction of 5-Hydroxy-6-methyl-pyridine-3,4-dicarboxylic Acid Diethyl Ester: Synthesis of Vitamin B$_6$

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**Abstract**: Alternative methods for the synthesis of pyridoxine have been investigated. The key intermediate, 5-hydroxy-6-methyl-pyridine-3,4-dicarboxylic acid diethyl ester (**5**), was reduced with either a silane monomer (MeSiH(OEt)$_2$) or a polysiloxane (polymethylhydrosiloxane, PMHS) to afford crude pyridoxine. An isolation technique utilizing a commercially available resin was devised, affording the desired product, vitamin B$_6$, in an overall yield of 38-54 % and a purity of 76%.

**Keywords:** Polymethylhydrosiloxane (PMHS), silanes, ester reduction, pyridoxine, vitamin B$_6$

## Introduction
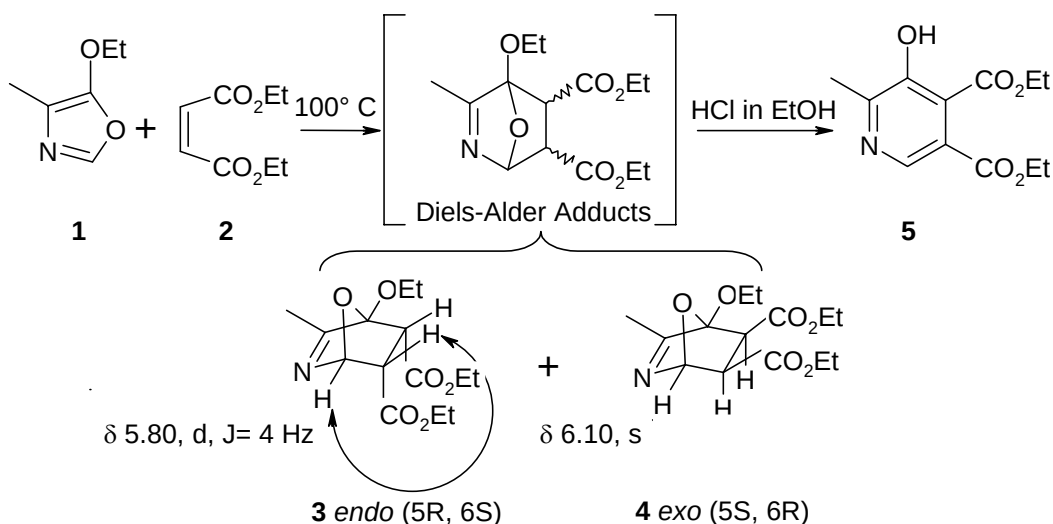
Vitamin B$_6$ is a water-soluble vitamin that is manufactured in bulk as pyridoxine hydrochloride. Vitamin B$_6$ is an important nutrient and plays an essential role in the body's amino acid biochemical pathways. As a consequence, it is found in a variety of vitamin preparations and is a common food additive. Because of its importance, the synthesis and commercial production of vitamin B$_6$ have been the subject of intense research for many years [1-2]. Currently, the preferred industrial synthesis of vitamin B$_6$ uses the Kondrat'eva approach [3-6], which combines a Diels-Alder reaction with a subsequent aromatization as the key step in forming the hydroxypyridine ring. Typically, the Diels-

Alder precursors are an oxazole diene and a dienophile, usually derived from 2-butene-1,4-diol. Derivatives of maleic and fumaric acids [7-16] are also good dienophiles for this reaction. A major disadvantage of using the unsaturated succinic acid approach is their cost. Excess equivalents of hydride reagents are required to reduce the two carboxylic groups, resulting in unacceptably large waste streams of inorganic salts. As a result no commercial process is based on this strategy.

## Results and Discussion

Using the method reported by Firestone and Harris [8], a neat mixture of 5-ethoxy-4-methyloxazole (**1**) and excess diethyl maleate (**2**) underwent a Diels-Alder cycloaddition to afford a mixture of bridged intermediates -*endo* (5R,6S)- and *exo* (5S,6R)-4-ethoxy-3-methyl-7-oxa-2-azabicyclo[2.2.1]-hept-2-ene-5,6-dicarbocyclic acid diethyl esters (rac-**3** and rac-**4**). Although not necessary for the synthesis of the desired diester **5**, the rac-**3** *endo* and rac-**4** *exo* adducts could be separated by column chromatography and were characterized by NMR for the first time. The bridgehead proton of the rac-**3** *endo* isomer was observed as a doublet (*J*= 4Hz) at 5.80 ppm, which supports a dihedral angle of 45° with the adjacent proton. In the model of the rac-**4** *exo* isomer, this angle changes to approximately 90°, thus no splitting of the bridgehead proton is expected and indeed none was observed. In a typical reaction, the crude bicyclic adducts were not isolated, but instead were treated with HCl to facilitate aromatization. After a final treatment with sodium bicarbonate, a single achiral product, 5-hydroxy-6-methyl-pyridine-3,4-dicarboxylic acid diethyl ester (**5**), was isolated (Scheme 1).

**Scheme 1:** Synthesis of hydroxypyridine diester **5** using the Diels-Alder reaction
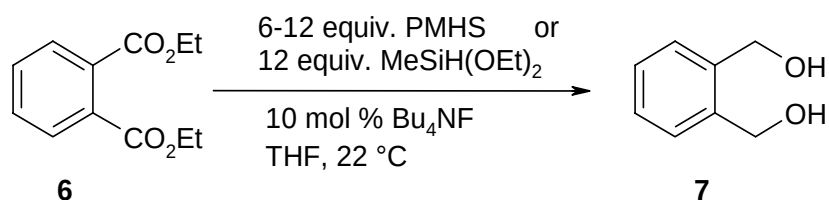
The reduction of hydroxypyridine diester (**5**) with stoichiometric metal hydride reagents like lithium aluminum hydride [17], sodium aluminum hydride [18], alkaline earth metal borohydrides [19] and lithium borohydride [20] is known. Thus, focus was placed on using silane reagents as an alternative approach for the complete reduction of the ester functional groups to the desired primary alcohols. These hydride reagents have not previously been applied in a synthesis of vitamin $B_6$.
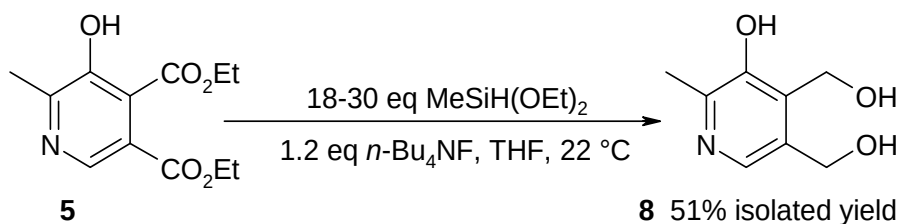
The catalyzed-hydrosilylation / reduction was considered based on several recent publications in journals and patents. The use of inexpensive silanes such as polymethylhydrosiloxane, PMHS, which is a by-product of the silicon industry, or alkoxysilanes, which can be synthesized from inexpensive chlorosilanes [21-27], was examined. A variety of catalysts can be used to activate the hydrosilylation: transition metals (especially Ti [28-31] and Zn [32-36]) or nucleophiles (especially metal hydroxides / alkoxides [37-41], and fluoride salts [42-55]). Because fluoride salts were reported to catalyze ester reductions at room temperature, this mild hydrosilylation / reduction method was investigated for the synthesis of vitamin $B_6$.

In a model experiment, diethyl phthalate (**6**) was easily reduced using Lawrence's conditions [50] (THF, 6 equiv. PMHS, 10 mol% *n*-Bu$_4$NF, 22 °C) to afford 1,2-benzenedimethanol (**7**) in 47% isolated yield (Scheme 2). The isolated yield was increased to 64% when 12 equiv. of PMHS were used. Replacing PMHS by 12 equiv. of the monomer silane, MeSiH(OEt)$_2$, afforded a comparable isolated yield of 62%. The model system was advantageous because the diol product (**7**) could be extracted into an organic solvent, and thus readily isolated. With this positive result, the conditions were then applied to the more challenging hydroxypyridine diester derivative (**5**).
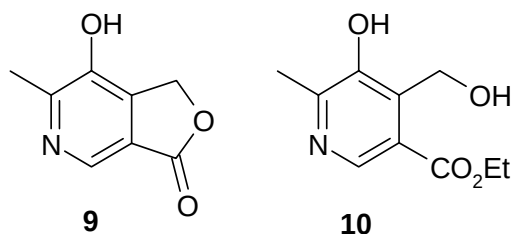
**Scheme 2:** Reduction of a model compound, diethyl phthalate (**6**)



Initially, the 5-hydroxy-6-methyl-pyridine-3,4-dicarboxylic acid diethyl ester (**5**) was not reduced under the mild conditions (either 8 equiv. PMHS or 7.5 equiv. MeSiH(OEt)$_2$ -10 mol%Bu$_4$NF in THF, 22 °C, 24 h; Table 1, entries 1 and 2). Additionally, under the PMHS conditions, large amounts of solids formed during the reaction. Reduction did occur at 22 °C when large excesses of the monomeric reducing reagent MeSiH(OEt)$_2$ (18-30 equiv.) and stoichiometric amounts of Bu$_4$NF (1.2 equiv.) were used (Scheme 3). No vitamin $B_6$ was isolated from the PMHS reactions and little or no starting material (**5**) was observed following the reaction. The desired vitamin $B_6$ product as a free base can serve as a multi-dentate ligand, capable of cross coupling with the polymeric backbone of PMHS and thus producing the observed solids. Such solidification was also observed by Mimoun and coworkers during reduction attempts on lactones [36], further supporting the claims of polymeric cross coupling.

**Scheme 3:** Reduction of 5-hydroxy-6-methyl-pyridine-3,4-dicarboxylic acid diethyl ester (**5**) at 22 °C



Not only was the desired product vitamin $B_6$ (**8**) covalently trapped on the polymer, but also mixtures of the partially reduced intermediates lactone (**9**) and mono reduced ester (**10**) (Figure 1). The trapping of these intermediates also contributed to the solidification of the reaction mixture.

**Figure 1:** Some partially reduced Vitamin $B_6$ intermediates



Use of the additive $Si(OEt)_4$ afforded a nearly homogeneous solution. It was proposed that the $Si(OEt)_4$ allowed for an exchange between the alkoxy groups of the vitamin $B_6$ free base (**8**) and the different silicon sites. Thus, a reduction in the amount of cross-coupled polymer was observed. However, use of this additive provided only modest yields under the PMHS conditions. A further disadvantage with the starting material, hydroxypyridine diester (**5**), was that the phenolic hydroxyl group also acted as a nucleophile and readily attached to the polysiloxane surface, further complicating the isolation of fully and partially reduced products.

A variety of conditions were screened and the results are reported in Table 1. The best conditions found for complete reduction utilized 10-15 equiv. $MeSiH(OEt)_2$, either neat or in dioxane, 10 mol% $Bu_4NF$ and 100 °C for *circa* 24 h (Table 1, exp. 10 and 13). These conditions afforded at best a 50-54% isolated yield of vitamin $B_6$ free base and up to 18% of the intermediates. These partially reduced products were either characterized by comparison to known compounds, lactone (**9**) [56], or observed in GC/MS experiments, mono reduced (**10**) (Figure 1). Based on another publication [57], $Bu_4NF$ was replaced by the combination of 10 mol% CsF and 20 mol% 18-crown-6 ether. It was proposed that this would increase the nucleophilicity of the fluoride as a "naked" anion and improve the reaction. However, under these modifications the reaction still required 24 h at 100 °C for completion and afforded a similar LC yield of 52% (Table 1, Exp. 14).

As stated previously, several difficulties were encountered in the isolation of vitamin $B_6$ after the silane reduction. An isolation method had to be developed in order to efficiently remove vitamin $B_6$ free base from the crude reaction mixture. The best purification approach consisted of adding EtOH to the reaction mixture in order to allow for fluoride-catalyzed exchange [50] between vitamin $B_6$ and EtOH on the silicon sites. The resulting reaction mixture was filtered over the strongly acidic resin Dowex 50-WX8, which retained vitamin $B_6$. The siloxanes and other by-products were easily eluted with EtOH. Then the desired product, vitamin $B_6$ free base (**8**), was eluted from the resin using a gradient of water and $NH_4OH$. Concentration of the combined fractions afforded vitamin $B_6$ as the free pyridoxine in an overall yield of 54% and a HPLC purity of 75.9 w/w% (weight/weight%, calibrated HPLC; Table 1, Exp. 13).

**Table 1:** Reduction of 5-hydroxy-6-methyl-pyridine-3,4-dicarboxylic acid diethyl ester (**5**).

| Conditions (silane reagent-catalyst, solvent, temperature, time) | Exp. | Overall yield[a] [LC yield] % | Purity % |
|---|---|---|---|
| 8 equiv. PMHS-10 mol% $Bu_4NF$ in THF, 22 °C, 24 h | **1** | 0 | |
| 7.5 equiv. $MeSiH(OEt)_2$-10 mol% $Bu_4NF$ in THF, 22 °C, 24 h | **2** | 0[b] | |
| 12 equiv. $Si(OEt)_4$-30 equiv. PMHS, 1.2 equiv. $Bu_4NF$ in THF, 22 °C, 24 h | **3** | 38 | 5.1 |
| 30 equiv. $MeSiH(OEt)_2$-1.2 equiv. $Bu_4NF$ in THF, 22 °C, 24 h | **4** | 51 | 9.2 |
| 8 equiv. $MeSiH(OEt)_2$-10 mol% $Bu_4NF$ in THF, reflux, 2 h | **5** | 0[b] | |
| 8 equiv. $MeSiH(OEt)_2$-10 mol% $Bu_4NF$ in THF, reflux, 96 h | **6** | [21][b] | |
| 16 equiv. PMHS-8 equiv. $Si(OEt)_4$-10 mol% $Bu_4NF$ in DMF, 150 °C, 24 h | **7** | [11][b,c] | |
| 8 equiv. $Si(OEt)_4$-8 equiv. PMHS-10 mol% $Bu_4NF$, 160 °C, 24 h | **8** | [9][d] | |
| 16 equiv. $MeSiH(OEt)_2$-1.2 equiv. $Bu_4NF$ in THF, 22 °C, 24 h | **9** | [60][b] | |
| 10 equiv. $MeSiH(OEt)_2$-10 mol% $Bu_4NF$, no solvent, 100 °C, 21 h* | **10** | 51 [60][b] | 55.8[e] |
| 15 equiv. $MeSiH(OEt)_2$-10 mol% $Bu_4NF$, no solvent, 100 °C, 21 h | **11** | 42 [60][b] | 65.2[f] |
| 15 equiv. $MeSiH(OEt)_2$-20 mol% $Bu_4NF$, no solvent, 100 °C, 26 h | **12** | 46 [65][b] | 64.8[f] |
| 15 equiv. $MeSiH(OEt)_2$-10 mol% $Bu_4NF$ in dioxane, 100 °C, 24 h* | **13** | 54 | 75.9 |
| 15 equiv. $MeSiH(OEt)_2$, 10 mol% CsF, 20 mol% 18-crown-6 ether, dioxane, 100 °C, 24 h | **14** | [52][b] | |

*Best conditions (highlighted in blue); [a] Weight yield x Purity; [b] incomplete reaction: partially reduced product(s) detected; [c] partially reduced product characterized as 5-hydroxy-pyridine lactone (**9**) (cyclization during work-up); [d] no change after 1 h, either decomposition of Si-H or not enough reagent; [e] partially reduced products (**9**) and (**10**) observed (18%); [f] partially reduced products (<6%)

**Conclusions**

5-Hydroxy-6-methyl-pyridine-3,4-dicarboxylic acid diethyl ester (**5**) was successfully reduced with silane reducing reagents. Cross-linking problems with PMHS made this reagent less attractive for the synthesis of vitamin $B_6$. Alkoxysilanes, when used in a fluoride-catalyzed hydrosilylation, allowed for the isolation of the desired fully reduced product. The isolation of free vitamin $B_6$ from the reaction mixture was best accomplished by using the resin Dowex 50-WX8.

Even though the fluoride-catalyzed hydrosilylation / reduction was possible, large excesses of the silane reducing reagent were required to yield reasonable amounts of fully reduced vitamin $B_6$. Although the yields were significantly lower than the classical hydride reduction methods, the described examples provide the first successful use of silanes for the reduction of a hydroxypyridine diester to the pyridoxine free base. Thus, the use of these reagents offers an alternative route to vitamin $B_6$. Further reduction of the required amount of silane, final product isolation techniques, as well as a recovery strategy for the silane waste stream still need to be further addressed. Additionally, recovery and full conversion of the partially reduced products to vitamin $B_6$ free base needs to be further developed in order to consider this methodology as a potential large scale production process. Investigations continue and will be reported in due course.

**Acknowledgements**

**Experimental**

*General*

All chemical reagents were purchased from Fluka. The reactions were monitored by GC (Perkin Elmer Auto System XL, RESTEK Rtx-5SilMS 30 m, 0.28 micron column) and HPLC (Hewlett Packard 1050, YMC Hydroxphere-C18, HS-303 column). The known partially reduced products 7-hydroxy-6-methyl-1H-furo[3,4-c]pyridine-3-one (**9**) and 4-hydroxymethyl-2.5-dimethylpyridin-3-ol (**10**) were observed by HPLC/MS (Hewlett Packard 1100MSD) and their structures confirmed by ^{1}H-NMR (Bruker Avance 400 MHz) for comparison to the literature data.

*Isolation of Diels-Alder adducts endo (5R,6S)-4-ethoxy-3-methyl-7-oxa-2-aza-bicyclo[2.2.1]hept-2-ene-5,6-dicarbocyclic acid diethyl ester (**3**) and exo (5S,6R)-4-ethoxy-3-methyl-7-oxa-2-aza-bicyclo[2.2.1]hept-2-ene-5,6-dicarbocyclic acid diethyl ester (**4**).*

5-Ethoxy-4-methyloxazole (**1**, 0.64 g, 5 mmol) and diethyl maleate (**2**, 1.72 g, 10 mmol) were heated neat in a round bottom flask under argon in an oil bath at 110 °C for 3 h. Chromatography of the crude Diels-Alder adducts on silica gel (EtOAc/hexane, 1:1) afforded 620 mg of the *endo* isomer rac-**3** (41%) and 360 mg of *exo* isomer rac- **4** (24%).

*Spectral and Analytical Data*

rac-**3**: $^1$H-NMR (CDCl$_3$, SiMe$_4$) δ 5.80 (d, *J* = 4 Hz, 1 H), 4.05-4.1 (m, 4 H), 3.75-3.9 (m, 2 H), 3.73 (dd, *J* = 10 Hz, *J* = 4 Hz, 1 H), 3.19 (d, *J* = 10 Hz, 1 H), 2.32 (s, 3 H), 1.2-1.35 (m, 9 H); $^{13}$C-NMR (CDCl$_3$) δ 179.33, 169.02, 167.84, 113.32, 88.14, 63.30, 61.17, 60.99, 51.15, 46.42, 16.91, 15.51, 14.21, 14.05. Analysis: Found C, 55.85; H, 6.75; N, 4.64; C$_{14}$H$_{21}$HO$_6$ requires C, 56.17; H, 7.07; N, 4.68.

rac-**4**: $^1$H-NMR (CDCl$_3$, SiMe$_4$) δ 6.10 (s, 1 H), 4.1-4.25 (m, 4 H), 3.8-3.9 (m, 1 H), 3.65-3.75 (m, 1 H), 2.8-2.9 (m, 2 H), 2.14 (s, 3 H), 1.2-1.35 (m, 9 H); $^{13}$C-NMR (CDCl$_3$) δ 177.89, 169.92, 168.74, 113.17, 89.42, 64.52, 61.69 (2 C), 50.89, 45.57, 15.67, 14.95, 14.57, 14.39. Analysis: Found C, 56.01; H, 6.80; N, 4.77; C$_{14}$H$_{21}$HO$_6$ requires C, 56.17; H, 7.07; N, 4.68.

*Hydrosilylation/reduction of hydroxypyridine diester* (**5**) *to vitamin B$_6$*

To a solution of 5-hydroxy-6-methyl-pyridine-3,4-dicarboxylic acid diethyl ester (**5**, 506 mg, 2 mmol) and diethoxymethylsilane (4.03 g, 30 mmol) in dioxane (1 mL) was added a solution of tetrabutylammonium fluoride (0.2 ml, 1 M, 0.2 mmol) in THF. The reaction mixture was heated in an oil bath at 100 °C for 24 h. The flask was removed from the oil bath and to the reaction mixture was added EtOH (100 mL). The mixture was allowed to cool and to further stir overnight. A glass-fritted filter (pore 2) was filled with Dowex 50-WX8, pre-washed three times with concentrated aqueous HCl and water to a pH of 6. The ethanolic crude reaction solution was filtered through the resin and the resin was rinsed successively with EtOH (100 mL), water (200 mL), 1% NH$_4$OH (200 mL), 4% NH$_4$OH (200 mL) and 25% NH$_4$OH (200 mL). Only the fraction obtained from the 4% NH$_4$OH elution contained vitamin B$_6$ free base. Concentration of the 4% NH$_4$OH fraction afforded 240 mg of crude vitamin B$_6$ (**8**) free base (HPLC purity 75.9 w/w%, isolated yield 54%).

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*Samples Availability:* Starting materials, intermediates and final products are all known compounds. Some are available from the author upon request.