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Synthesis of a 6-Methylpyridoxine Hydrochloride Derivative as an Electrophilic Precursor for Pyridoxal-like Functionalization

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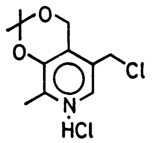
Synopsis. Through a key step of regioselective rearrangement of 5′-*O*-acetyl-3,4′-*O*-isopropylidene-6-methylpyridoxine 1-oxide, stable 5′-deoxy-2′,5′-dichloro-3,4′-*O*-isopropylidene-6-methylpyridoxine hydrochloride, which is expected to be a strong electrophile in an HCl free form, was synthesized from DL-alanine in good yield.

In relation to our systematic studies on the utilization of 2′- and/or 5′-chloropyridoxine derivatives as the electrophilic precursors for pyridoxal-like functionalization, the synthesis and electrophilic reactivity to thiols and sulfonamides have been successfully exemplified in the cases of 5′-deoxy-5′-chloro-3,4′-*O*-isopropylidenepyridoxine hydrochloride (**1**),[1] 5′-deoxy-2′-chloro-3,4′-*O*-isopropylidenepyridoxine hydrochloride (**2**),[1] and 5′-deoxy-2′,5′-dichloro-3,4′-*O*-isopropylidenepyridoxine hydrochloride (**3**).[2] Here we describe a synthetic method of 5′-deoxy-2′,5′-dichloro-3,4′-*O*-isopropylidene-6-methylpyridoxine hydrochloride (**4**) as an alternative precursor, required for completion of our present project. This method was characterized by novel regioselective isopropylidenation of **5** and regioselective rearrangement of an intermediate *N*-oxide (**8**).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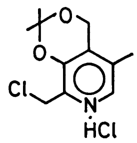
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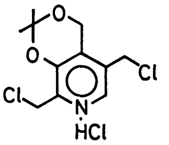
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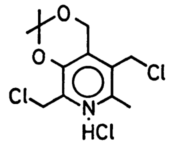
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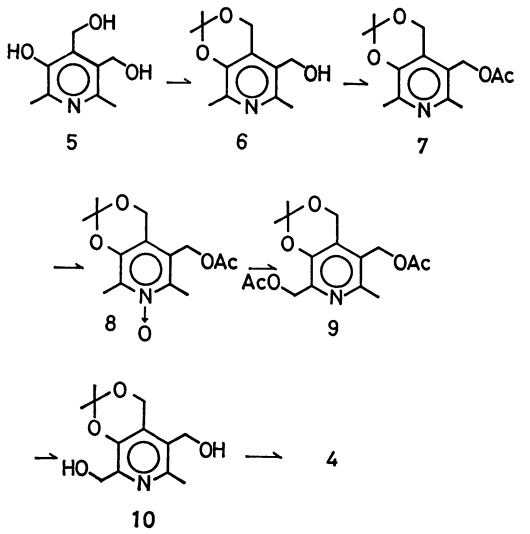

Synthesis began with 6-methylpyridoxine (**5**), which was prepared in good yield by the method previously reported.[3] Treatment of **5** with acetone saturated with hydrogen chloride gave 3,4′-*O*-isopropylidene-6-methylpyridoxine hydrochloride regioselectively, which was neutralized to yield the corresponding HCl free form (**6**). The usual acetylation of **6** with acetic anhydride and pyridine afforded 5′-*O*-acetyl-3,4′-*O*-isopropylidene-6-methylpyridoxine (**7**), which was, then, oxidized with *m*-chloroperbenzoic acid to give 5′-*O*-acetyl-3,4′-*O*-isopropylidene-6-methylpyridoxine 1-oxide (**8**). Rearrangement of **8** with acetic anhydride in chloroform regioselectively gave 2′-acetoxy-5′-*O*-acetyl-3,4′-*O*-isopropylidene-6-methylpyridoxine (**9**). Compound **9** was successfully deacetylated by treatment with sodium methoxide in methanol followed by neutralization with solid carbon dioxide and extraction with ethyl acetate to afford 2′-hydroxy-3,4′-*O*-isopropylidene-6-methylpyridoxine (**10**). This was successfully chlorinated with thionyl chloride in benzene to yield **4**.

The regioselectivity in isopropylidenation of **5** is due probably to the concentration of hydrogen chloride as was established in the previous report.[4] As reported by Traynelis and Pacini[5a] and others,[5b,c] the rearrangement of pyridine 1-oxide with acetic anhydride occurs intramolecularly through a rate-controlling conversion of 1-acetoxy-2-methylpyridinium ion to an anhydrobase by proton abstraction. Therefore, facility of proton release from either methyl group at C_2 or C_6 in **8** determines the product. Since C_6-methyl protons always appear at lower field in ^1H NMR spectra (Table 1) than C_2-methyl protons and are interacting with a neighboring acetyl carbonyl group at C_5, release of a proton from C_6-methyl group seems less favorable than that from a C_2-methyl group.

TABLE 1. ^1H NMR SPECTRAL DATA OF 6-METHYLPYRIDOXINE DERIVATIVES
(δ ppm, IN $CDCl_3$ AT AMBIENT TEMPERATURE)

Compound	$C(\underline{CH_3})_2$	$-CO\underline{CH_3}$	$C_2-\underline{CH_3}$	$C_6-\underline{CH_3}$	$^{5'}\underline{CH_2}-O$	$^{4'}\underline{CH_2}-O$	$^{2'}\underline{CH_2}-O$
6	1.53	—	2.36	2.44	4.58	4.59	—
7	1.54	2.06	2.39	2.51	5.00	4.91	—
8	1.57	2.07	2.45	2.56	5.00	4.95	—
9	1.54	a)	—	2.55	5.01	4.95	5.18
10	1.53	—	—	2.55	4.63	4.99	4.63

a) $^{5'}C-O-CO\underline{CH_3}$ at 2.07 and $^{2'}C-O-CO\underline{CH_3}$ at 2.12 ppm.

Utilization of **4** as a precursor for an electrophilic construction unit will be reported elsewhere.

Experimental

The ^{1}H NMR spectra were recorded on a Japan Electron Optics Laboratory JEOL FX-400 apparatus with TMS as the internal standard in chloroform-*d* and the chemical shift was represented by δ. IR spectra were recorded on a Shimadzu IR-27 instrument. Merck silica gel 60 (Art. 7734, 0.063—0.20 mm) was used for the column chromatography and Wakogel B-5 FM (Wako Pure Chem. Co., Ltd.) for the thin layer chromatography (TLC), in which product spots were visualized in an iodine-vapor bath. The mp are uncorrected, measured in a bilayered cover glass (18 m/m) with micro melting point apparatus (Yanagimoto Seisakusho, serial No. 2647). Solvent system: benzene: ethyl acetate, 3:2 v/v (solvent A) and 9:1 v/v (solvent B). 6-Methylpyridoxine (**5**) was prepared by the method described in Ref. 3, in good yield from DL-alanine and dimethyl maleate.

Preparation of 3,4′-O-Isopropylidene-6-methylpyridoxine (**6**). A suspended mixture of 10.34 g of **5** in 200 ml of dry acetone was saturated with hydrogen chloride while being stirred and cooled in an ice-bath. Then, the flask was allowed to stand in a refrigerator overnight. After 500 ml of diethyl ether was mixed and stirred into the flask, the resulting colorless precipitate (hydrochloride) was collected by filtration. The hydrochloride of **6** dissolved in a minimum amount of water was neutralized by portional addition of sodium hydrogencarbonate saturated in water followed by extraction with chloroform to give 10 g of **6** as a colorless liquid, which spontaneously crystalized; mp 141.5—143 °C. Found: C, 64.09; H, 7.63; N, 5.93%. Calcd for $C_{12}H_{17}O_3N$: C, 64.55; H, 7.68; N, 6.27%. ^{1}H NMR data are listed in Table 1. IR (KBr disk) ν 3180, 3000, 2940, 1601, 1440, 1386, 1375, 1280, 1245, 1200, 1146, 1104, 1069, 1040, 1024, 996, 983, 875, 867, 795, 703, 676, 564, 530, and 497 cm^{-1} as characteristic bands.

Preparation of 5′-O-Acetyl-3,4′-O-isopropylidene-6-methylpyridoxine (**7**). To a solution of 3.077 g of **6** in 15 ml of pyridine, 15 ml of acetic anhydride was added all at once while being stirred. After subsequent stirring at the ambient temperature for 1 h, the mixture was poured into water (*ca.* 200 ml) and, then, extracted with chloroform, which was dried over $MgSO_4$ and filtered through Celite (No. 545). The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel (200 g) column, eluted with solvent A, to give 3.29 g of **7** (90% yield); colorless liquid, R_f 0.7 (solvent A). Found: C, 63.61; H, 7.10; N, 5.18%. Calcd for $C_{14}H_{19}O_4N$: C, 63.38; H, 7.22; N, 5.28%. ^{1}H NMR data are listed in Table 1. IR (KRS neat) $\nu_{C=O}$ 1738 cm^{-1}.

Preparation of 5′-O-Acetyl-3,4′-O-isopropylidene-6-methylpyridoxine 1-Oxide (**8**). To 0.37 g of **7** in 10 ml of chloroform, 0.283 g of 85% pure *m*-chloroperbenzoic acid was added portion by portion at the ambient temperature. The reaction was monitored by TLC until **7** disappeared. The reaction mixture was neutralized by addition of sodium acetate after addition of 10 ml of water. After the usual work-up, 0.34 g (87% yield) of **8** was obtained by chromatography (solvent A) as a colorless liquid; R_f 0.2 (solvent A). ^{1}H NMR data are listed in Table 1. IR (KRS neat) $\nu_{C=O}$ 1740; ν 1560, 1490, 1375, 1300, 1220, 1130, 1070, 1025, 878, 828, and 581 cm^{-1} as characteristic bands. Found: C, 59.24; H, 6.64; N, 4.64%. Calcd for $C_{14}H_{19}O_5N$: C, 59.77; H, 6.81; N, 4.98%.

Preparation of 2′-Acetoxy-5′-O-acetyl-3,4′-O-isopropylidene-6-methylpyridoxine (**9**). A solution of 0.3 g of **8** in 2 ml of acetic anhydride and 5 ml of chloroform was heated at 50 °C for 20 min. After removal of solvents under reduced pressure, the residue was chromatographed on a silica gel (20 g) column, eluted with solvent A, to afford 0.304 g (88% yield) of **9** as colorless liquid; R_f 0.7 (solvent A). Found: C, 59.43; H, 6.48; N, 4.14%. Calcd for $C_{16}H_{21}O_6N$: C, 59.43; H, 6.55; N, 4.33%. ^{1}H NMR data are summarized in Table 1. IR (KRS neat) ν 1740, 1440, 1378, 1282, 1220, 1145, 1112, 1025, 965, 870, 792, and 605 cm^{-1} as characteristic bands.

Preparation of 2′-Hydroxy-3,4′-O-isopropylidene-6-methylpyridoxine (**10**). To a sodium methoxide solution, which was prepared by addition of 0.05 g of metal sodium to 10 ml of methanol, 0.266 g of **9** in 5 ml of methanol was added dropwise. The reaction was completed immediately. The mixture was neutralized by portional addition of pieces of solid carbon dioxide. After removal of the solvent, the residue was triturated with ethyl acetate followed by filtration through Celite (No. 545). The filtrate was evaporated under reduced pressure followed by recrystallization from ethanol to give 0.15 g (76% yield) of **10**; colorless plates, mp 168.5—170 °C. Found: C, 60.30; H, 7.25; N, 5.76%. Calcd for $C_{12}H_{17}O_4N$: C, 60.24; H, 7.16; N, 5.85%. ^{1}H NMR data are listed in Table 1. IR (KBr disk) ν 3320, 3050, 2990, 2940, 2880, 2760, 1595, 1570, 1430, 1382, 1370, 1280, 1265, 1202, 1140, 1105, 1040, 1015, 1002, 990, 958, 940, 872, 800, 743, 676, 655, 635, 597, 535, and 490 cm^{-1} as characteristic bands. R_f 0.5 ($CHCl_3$: methanol 9:1 v/v).

Preparation of 5′-Deoxy-2′,5′-dichloro-3,4′-O-isopropylidene-6-methylpyridoxine Hydrochloride (**4**). To a suspended mixture of 2.33 g of **10** in 40 ml of benzene, 1.41 ml of thionyl chloride in 10 ml of benzene was added dropwise, resulting in coagulation and, then, a transparent solution without color change. After stirred for 30 min at ambient temperature, 50 ml of diethyl ether was added for precipitation. The precipitate was collected by filtration and washed several times with diethyl ether to give 2.643 g (87% yield) of **4.** A part of the product was recrystallized from acetone for analytical use; colorless crystals, mp 143 °C (browning with melt) —150 °C (decomposed with evolving gas) and —162 °C (complete melt and decomposition with browning and resulting in viscous liquid). Found: C, 46.29; H, 5.22; N, 4.48; Cl, 34.02%. Calcd for $C_{12}H_{16}O_2NCl_3$: C, 46.10; H, 5.16; N, 4.48; Cl, 34.02%. IR (KBr disk) ν 3020, 2960, 2350, 1960, 1632, 1540, 1470, 1430, 1417, 1377, 1365, 1312, 1285, 1253, 1204, 1135, 1110, 1075, 1050, 1010, 990, 980, 967, 943, 925, 912, 850, 838, 736, 721, 649, 618, 552, 492, and 425 cm^{-1} as characteristic bands.

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