A NOVEL SYNTHESIS OF A HIGHLY STERICALLY HINDERED C_2-SYMMETRIC CHIRAL PYRIDINE DERIVATIVE

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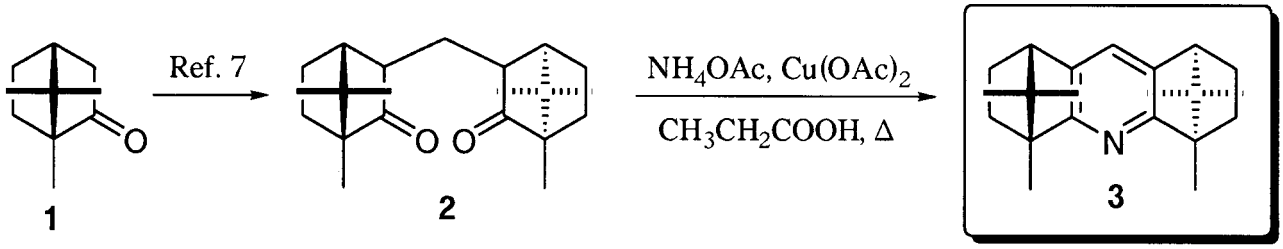
Abstract --- A highly sterically hindered C_2-symmetric chiral pyridine derivative (**3**) was synthesized from 1,5-diketone (**2**) by the action of $NH_4OAc/Cu(OAc)_2$ in refluxing propionic acid. The pK_a of **3** was determined to be 6.26 and the structure was characterized by X-Ray crystallographic analysis of its triflic acid salt.

Sterically crowded nitrogen molecules are gathering considerable attention from synthetic chemists due to their convenience as non-nucleophilic organic bases. As a typical example, *N,N*-diisopropylethylamine (DIPEA), known as a Hünig's base, is widely used in several types of organic transformation, such as esterification, alkylation, enolization, and protection.[1] A similarly important class of compounds, nitrogen heterocyclic derivatives such as pyridines, are also very attractive due to their lower basicity (*e.g.*, 2,6-di-*tert*-butylpyridine, aqueous pK_a 3.58[2]) relative to DIPEA (pK_a 18.1 in acetonitrile).[3] These compounds also play a pivotal role in the fields of asymmetric synthesis[4] and coordination[5] and supramolecular chemistry.[6]

A recent report[7] on the use of non-aldolizable ketones to derive 1,5-diketones focused our attention on the possibility of applying this method to design a new class of sterically hindered chiral pyridine derivatives, since 1,5-diketones are the well-known precursors for pyridine synthesis.[8] In this paper, we describe a novel synthesis of the highly sterically hindered C_2-symmetric chiral pyridine derivative (**3**) from (+)-camphor (**1**) via 1,5-diketone (**2**) (**Scheme 1**).[9, 10]



Scheme 1

Dedicated to Professor Teruaki Mukaiyama on the occasion of his 73rd birthday.

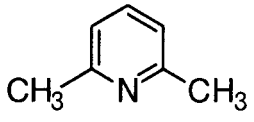
To construct a pyridine ring from 1,5-diketone (**2**), we first examined the possibility of using a dioxime strategy, which was recently developed by one of us.[11] However, despite our extensive efforts, even using a high-pressure technique,[12] no appreciable amount of the corresponding dioxime was obtained. After numerous trials with alternative procedures, we were delighted to find that ammonium salt in the presence of cupric acetate[13] was satisfactory for effecting the desired cyclization (**Table 1**). Thus, the best result was achieved using 10 equiv. of ammonium acetate and 3 equiv. of cupric acetate in refluxing propionic acid, which gave the desired chiral pyridine (**3**), mp 121.5-122.5 °C (sublimed); $[\alpha]_D^{26}$ +77.3° (c = 1.00, MeOH), in an isolated yield of 44% (entry 7).[14]

Table 1. Preparation of chiral pyridine (**3**) from 1,5-diketone (**2**).

Entry	Reagents (equiv.)	Conditions	Yield of **3** (%)[a]
1	$HCOONH_4$ (5), $Cu(OAc)_2$ (3)	AcOH, reflux, 44 h[b]	17 (50)
2	$HCOONH_4$ (5), $Cu(OAc)_2$ (3)	AcOH, reflux, 135 h[c]	7
3	NH_4OAc (5), $Cu(OAc)_2$ (3)	AcOH, reflux, 51 h[b]	20
4	NH_4OAc (10), $Cu(OAc)_2$ (3)	AcOH, reflux, 192 h[c]	32
5	NH_4OAc (10), $Cu(OAc)_2$ (3)	AcOH, 100 °C, 65 h[c]	17
6	NH_4OAc (10), $Cu(OAc)_2$ (3)	AcOH, reflux, MS3A, 34 h[c]	5
7	**NH_4OAc (10), $Cu(OAc)_2$ (3)**	**CH_3CH_2COOH, reflux, 162 h[c]**	**44** ⇐

[a] Isolated yield. Yield in parenthesis is recovered **2**. [b] Under N_2. [c] Under air.

The beautifully C_2-symmetric character of **3** was determined based on its ^1H and ^{13}C NMR measurements. The basicity of this compound, pK_a 6.26, was determined as half-neutralization potentials by titration at 25 °C with 0.10 M perchloric acid in acetic acid.[15] Despite the well-known fact that the introduction of an alkyl group increases the basicity of pyridines, **3** is a relatively weak base compared with other homologs: pK_a 6.72 for **4**,[16] 7.91 for **5**,[16] 8.75 for **6**,[16] and 8.09 for **7**.[17] This result suggests the significant shielding around the nitrogen-atom of **3** by bulky bornane skeletons.



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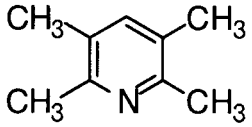

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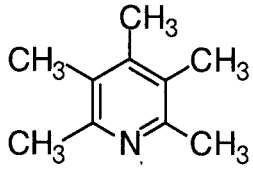

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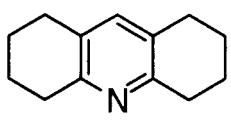

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In accordance with this observation, compound (**3**) showed no remarkable nucleophilic reactivity toward methyl iodide, acetyl chloride, acetic acid, or hydrochloric acid. However, it did react smoothly with trifluoromethanesulfonic acid (triflic acid) to form the crystalline salt (**8**), the structure of which was characterized by X-Ray crystallographic analysis. The ORTEP depiction of this complex is shown in **Figure 1**. Evidently, the triflate anion is captured into the molecular cleft surrounded by the adjacent bridgehead methyl groups.[18]

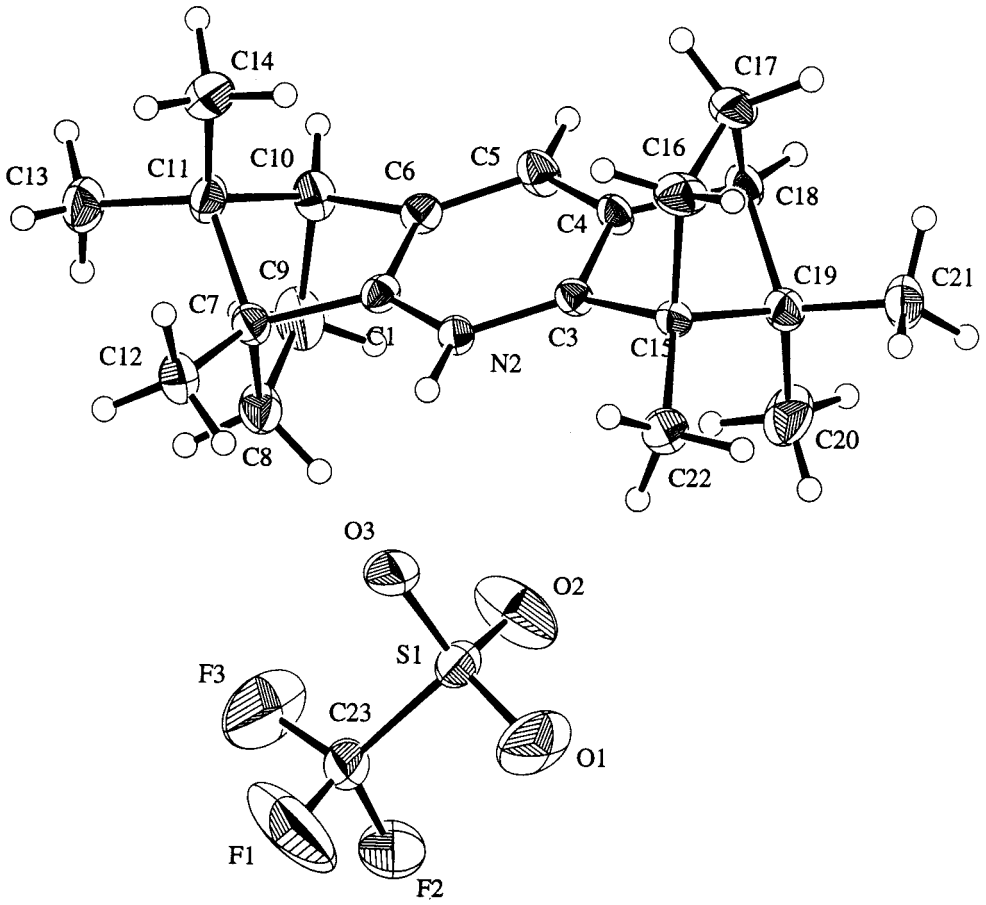
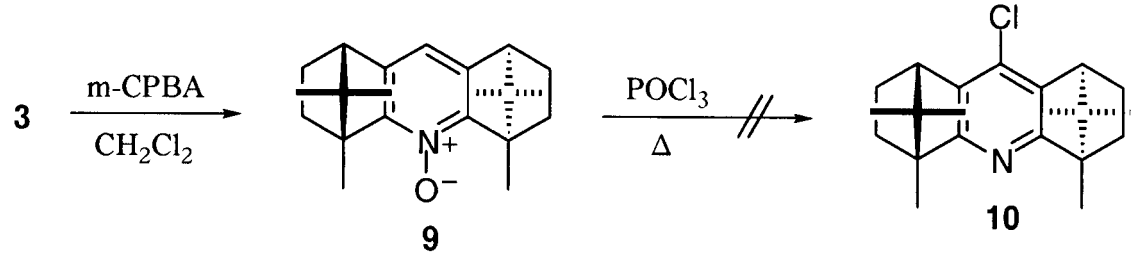


Figure 1. X-Ray crystal structure of the triflate complex (**8**). The distance between N(2) and O(3) is 2.928 Å; the distance between N(2) and H is 0.95 Å; the distance between O(3) and H is 2.101 Å.

To enhance the coordinating ability of **3** and evaluate its potential utility as a chiral (catalytic) base, we manipulated the pyridine ring by inserting an electron-donating group at the vacant 9-position of the pyridine ring. Unfortunately, **3** was not susceptible to normal electrophilic substitution, and the use of the corresponding *N*-oxide (**9**),[19] prepared by oxidation with *m*-chloroperbenzoic acid, was also fruitless: neither chlorination (heating with phosphorus oxychloride) nor nitration was observed due to the serious decomposition of **9** (**Scheme 2**). Since all of our efforts to elaborate the pyridine rings failed, further studies with compound (**3**) were abandoned.



Scheme 2

In conclusion, we have succeeded in preparing the highly sterically hindered C_2-symmetric chiral pyridine (3) by reacting diketone (2) with $NH_4OAc/Cu(OAc)_2$. The basicity of this compound was determined to be pK_a 6.26. Its characteristic behavior with triflic acid and the X-Ray crystallographic analysis of its salt reflect the proton sponge-like property[20] of 3. Further studies on the modification of the ligand design and its application to asymmetric synthesis are underway.

EXPERIMENTAL

All melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a JEOL LA-400 (400 MHz for ^1H and 100 MHz for ^{13}C NMR analysis) spectrometer. All NMR spectra were taken in $CDCl_3$ solutions and are reported in parts per million (δ) downfield from TMS, which was used as an internal standard. The FT-IR spectra (cm^{-1}) were measured with a JASCO Model FT/IR-5300 Fourier transform infrared spectrophotometer and the UV spectra (nm) were measured with a JASCO UVIDEC-670 spectrophotometer. Optical rotations were measured on a JASCO DIP-370 polarimeter. TLC was conducted using Merck precoated kieselgel 60F-254 plates (0.25 mm). Preparative TLC was carried out on 2 mm-thick Merck kieselgel 60PF-254.

Preparation of (1*S*, 4*R*, 5*R*, 8*S*)-1,4:5,8-Dimethano-4,5-dimethyl-11,11,12,12-tetramethyl-1,2,3,4,5,6,7,8-octahydroacridine (3).

A solution of diketone (2)[7] (200 mg, 0.63 mmol), ammonium acetate (486 mg, 6.3 mmol), and cupric acetate (377 mg, 1.89 mmol) in 2 mL of propionic acid was refluxed under air for 162 h. After cooling to 0 ℃, the mixture was diluted with water, basified with 50% aq NaOH, and extracted with Et_2O. The combined extracts were washed with brine, dried over K_2CO_3, and concentrated. The crude product was purified by preparative TLC (hexane / AcOEt = 9 : 1) to give 3 (81 mg, 44 %) as colorless crystals: R_f 0.66 (hexane / AcOEt = 9 : 1); mp 121.5-122.5 °C (from MeOH, sublimed); $[\alpha]_D^{26}$ +77.3° (*c* = 1.85, MeOH); UV (MeOH) λ_{max} (ε) 285 (31000), 230 (7500); FTIR (KBr) ν 1593, 1570, 1468, 1447, 1400; ^1H NMR ($CDCl_3$) δ 0.51 (6H, s), 0.94 (6H, s), 1.05 (2H, ddd, *J* = 12.5, 9.3, 3.7 Hz), 1.17 (2H, ddd, *J* = 12.2, 9.3, 3.7 Hz), 1.32 (6H, s), 1.78 (2H, ddd, *J* = 12.2, 10.0, 3.7 Hz), 2.05 (2H, ddt, *J* = 12.5, 10.0, 3.7 Hz), 2.72 (2H, d, *J* = 3.7 Hz), 7.07 (1H, s); ^{13}C NMR ($CDCl_3$) δ 10.6 (×2), 19.4 (×2), 20.0 (×2), 26.5 (×2), 32.1 (×2), 51.7 (×2), 53.8 (×2), 56.8 (×2), 121.9 (×2), 137.7, 165.8 (×2). *Anal.* Calcd for $C_{21}H_{29}N$: C, 85.37; H, 9.89; N, 4.74. Found: C, 85.51; H, 10.07; N, 4.81.

Basicity Determination. According to the procedure described in the literature,[15] the basicity of 3 was determined by potentiometric titration with a HORIBA Model F-22.

X-Ray Crystallographic Analysis of the Triflate Complex (8).

The required complex was prepared as follows: To a solution of 3 (100 mg, 0.33 mmol) in dry Et_2O (3 mL) was added dropwise TfOH (50 mg, 0.33 mmol) at 0 ℃, and the mixture was stirred for 10 min. After evaporation of the solvent, the residue was recrystallized from MeOH. Crystal data of 8:

$C_{22}H_{30}NO_3F_3S$, M= 445.54, monoclinic, space group $P2_1$ (#4), a = 10.460(2) Å, b = 10.693(3) Å, c = 11.199(2) Å, V = 1110.4(3) Å^3, Z = 2, D_{calc} = 1.332 g / cm^3, μ(Mo-Kα) = 1.93 cm^{-1}, number of observations 1915 ($I > 2.00\ \sigma(I)$), R = 0.068, R_W = 0.082. Intensity data were collected on a Rigaku RAXIS-IV diffractometer using Mo-Kα radiation (λ = 0.71070 Å).

Preparation of (1*S*, 4*R*, 5*R*, 8*S*)-1,4:5,8-Dimethano-4,5-dimethyl-11,11,12,12-tetramethyl-1,2,3,4,5,6,7,8-octahydroacridine *N*-Oxide (9).

To a solution of **3** (100 mg, 0.34 mmol) in CH_2Cl_2 (2 mL) was added m-CPBA (80% activity, 88 mg, 0.51 mmol) at 0 ℃, and the mixture was stirred for 12 h at rt. The mixture was quenched with 40% aq $Na_2S_2O_3$ and extracted with Et_2O. The extracts were washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by preparative TLC ($CHCl_3$ / MeOH = 9 : 1) to give **9** (91 mg, 86 %) as colorless crystals: R_f 0.81 ($CHCl_3$ / MeOH = 9 : 1); mp 140.0-140.5 ℃ (from MeOH, sublimed); $[\alpha]_D^{26}$ —2.88° (c = 0.69, MeOH); UV (MeOH) λ_{max} (ε) 297 (51000), 258 (1500), 226 (5800); FTIR (KBr) ν 1584, 1476, 1451, 1416, 1306, 1260; ^{1}H NMR ($CDCl_3$) δ 0.67 (6H, s), 0.91 (6H, s), 1.09 (2H, ddd, J = 12.7, 9.0, 3.9 Hz), 1.55 (2H, ddd, J = 12.9, 9.0, 3.9 Hz), 1.66 (6H, s), 1.83 (2H, ddd, J = 12.9, 9.8, 3.9 Hz), 2.08 (2H, ddt, J = 12.7, 9.8, 3.9 Hz), 2.76 (2H, d, J = 3.9 Hz), 6.89 (1H, s); ^{13}C NMR ($CDCl_3$) δ 12.9 (×2), 18.8 (×2), 20.3 (×2), 26.2 (×2), 31.5 (×2), 52.0 (×2), 55.4 (×2), 57.5 (×2), 115.9 (×2), 143.5, 152.3 (×2). *Anal.* Calcd for $C_{21}H_{29}NO{\bullet}H_2O$: C, 76.55; H, 9.48; N, 4.25. Found: C, 76.87; H, 9.05; N, 4.05.

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