

A NOVEL SYNTHESIS OF A HIGHLY STERICALLY HINDERED C₂-SYMMETRIC CHIRAL PYRIDINE DERIVATIVE

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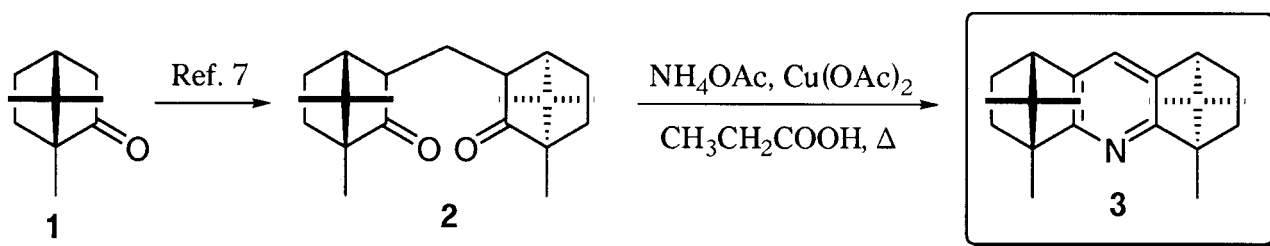
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Abstract --- A highly sterically hindered C₂-symmetric chiral pyridine derivative (3) was synthesized from 1,5-diketone (2) by the action of NH₄OAc/Cu(OAc)₂ in refluxing propionic acid. The pK_a of 3 was determined to be 6.26 and the structure was 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 3.58²) relative to DIPEA (pK_a 18.1 in acetonitrile).³ These compounds also play a pivotal role in the fields of asymmetric synthesis⁴ and coordination⁵ and supramolecular chemistry.⁶

A recent report⁷ 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 C₂-symmetric chiral pyridine derivative (3) from (+)-camphor (1) via 1,5-diketone (2) (**Scheme 1**).^{9, 10}



Scheme 1

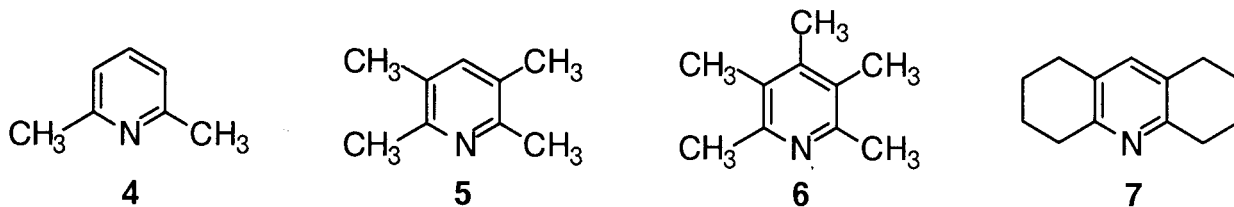
To construct a pyridine ring from 1,5-diketone (**2**), we first examined the possibility of using a dioxime strategy, which was recently developed by one of us.¹¹ However, despite our extensive efforts, even using a high-pressure technique,¹² no appreciable amount of the corresponding dioxime was obtained. After numerous trials with alternative procedures, we were delighted to find that ammonium salt in the presence of cupric acetate¹³ 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); $[\alpha]_D^{26} +77.3^\circ$ ($c = 1.00$, 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 ₄ OAc (5), Cu(OAc) ₂ (3)	AcOH, reflux, 51 h ^b	20
4	NH ₄ OAc (10), Cu(OAc) ₂ (3)	AcOH, reflux, 192 h ^c	32
5	NH ₄ OAc (10), Cu(OAc) ₂ (3)	AcOH, 100 °C, 65 h ^c	17
6	NH ₄ OAc (10), Cu(OAc) ₂ (3)	AcOH, reflux, MS3A, 34 h ^c	5
7	NH₄OAc (10), Cu(OAc)₂ (3)	CH₃CH₂COOH, reflux, 162 h^c	44 ⇌

^a Isolated yield. Yield in parenthesis is recovered **2**. ^b Under N₂. ^c Under air.

The beautifully *C*₂-symmetric character of **3** was determined based on its ¹H and ¹³C NMR measurements. The basicity of this compound, p*K*_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: p*K*_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.



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

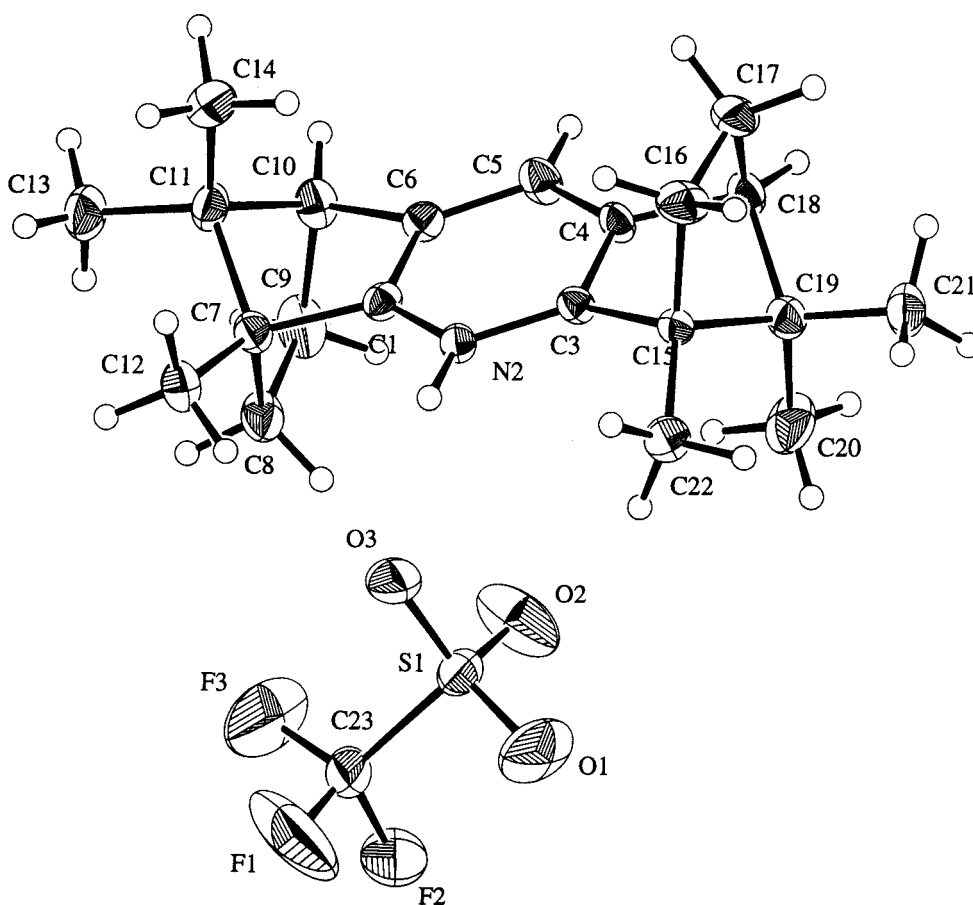
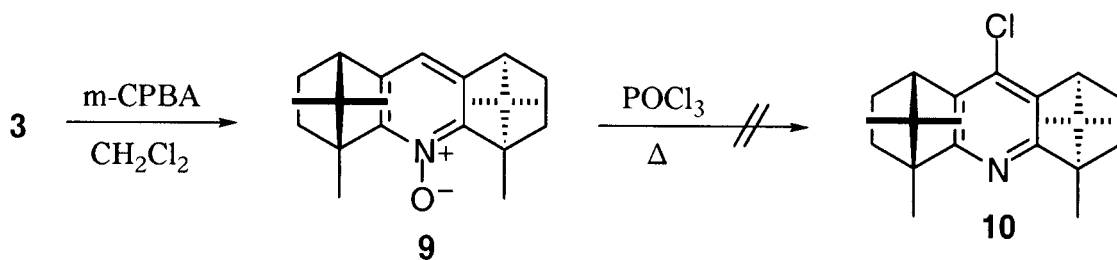


Figure 1. X-Ray crystal structure of the triflate complex (8). The distance between N(2) and O(3) is 2.928 Å; the distance between N(2) and H is 0.95 Å; the distance between O(3) and H is 2.101 Å.

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 $\text{NH}_4\text{OAc}/\text{Cu}(\text{OAc})_2$. The basicity of this compound was determined to be $\text{p}K_a$ 6.26. Its characteristic behavior with triflic acid and the X-Ray crystallographic analysis of its salt reflect the proton sponge-like property²⁰ 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 °C, 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); $[\alpha]_D^{26} +77.3^\circ$ (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 ($\times 2$), 19.4 ($\times 2$), 20.0 ($\times 2$), 26.5 ($\times 2$), 32.1 ($\times 2$), 51.7 ($\times 2$), 53.8 ($\times 2$), 56.8 ($\times 2$), 121.9 ($\times 2$), 137.7, 165.8 ($\times 2$). *Anal.* Calcd for $\text{C}_{21}\text{H}_{29}\text{N}$: 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 °C, 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, $V = 1110.4(3)$ Å³, $Z = 2$, $D_{\text{calc}} = 1.332$ g / cm³, $\mu(\text{Mo-K}\alpha) = 1.93$ 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-K α radiation ($\lambda = 0.71070$ 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 °C, and the mixture was stirred for 12 h at rt. The mixture was quenched with 40% aq $\text{Na}_2\text{S}_2\text{O}_3$ 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 / $\text{MeOH} = 9 : 1$) to give **9** (91 mg, 86 %) as colorless crystals: R_f 0.81 (CHCl_3 / $\text{MeOH} = 9 : 1$); mp 140.0-140.5 °C (from MeOH , sublimed); $[\alpha]_D^{26} -2.88^\circ$ ($c = 0.69$, MeOH); UV (MeOH) λ_{max} (ϵ) 297 (51000), 258 (1500), 226 (5800); FTIR (KBr) ν 1584, 1476, 1451, 1416, 1306, 1260; ^1H 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 ($\times 2$), 18.8 ($\times 2$), 20.3 ($\times 2$), 26.2 ($\times 2$), 31.5 ($\times 2$), 52.0 ($\times 2$), 55.4 ($\times 2$), 57.5 ($\times 2$), 115.9 ($\times 2$), 143.5, 152.3 ($\times 2$). *Anal.* Calcd for $\text{C}_{21}\text{H}_{29}\text{NO} \cdot \text{H}_2\text{O}$: C, 76.55; H, 9.48; N, 4.25. Found: C, 76.87; H, 9.05; N, 4.05.

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