A Convenient Synthesis of 2,2′,6,6′-Tetramethyl-4,4′-bipyridine and Its Oxidation to 2,2′,6,6′-Tetracarboxy-4,4′-bipyridine[1]

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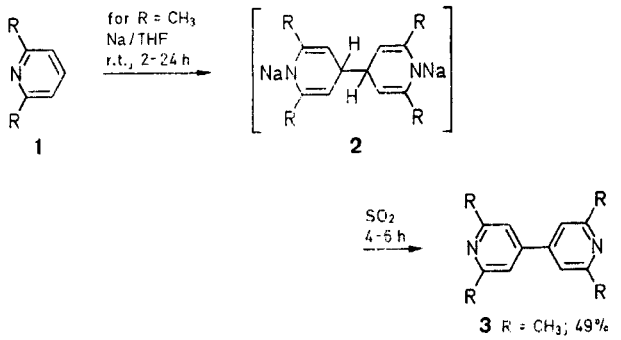
By reaction of 2,6-dimethylpyridine (**1b**) with sodium the tetrahydro-4,4′-bipyridine bis-sodium salt **2b** is formed. Of different dehydrogenation reagents tested, only sulfur dioxide affords the title compound **3b**, in 49% overall yield. By oxidation of **3b** with chromium trioxide, 2,2′,6,6′-tetracarboxy-4,4′-bipyridine (**3c**, 70%) is produced, a valuable precursor for several 2,2′,6,6′-tetrasubstituted 4,4′-bipyridines, e.g., the corresponding acid chloride **3d** and the carboxylic esters **3e** and **3f**.

Crown ethers containing a pyridine moiety linked in the 2,6-position have proven to be valuable complexing agents for cations with specific selectivities.[2] Corresponding biscrown ethers derived from 2,2′,6,6′-tetracarboxy-4,4′-bipyridine are reversible redox systems, for which complexation constants for several cations increase dramatically on reduction.[1]

For these new ligands, 2,2′,6,6′-tetramethyl-4,4′-bipyridine (**3b**) serves as indispensable starting material, for which we herewith describe a convenient synthesis.

The various but tedious laboratory syntheses for 4,4′-bipyridine (**3a**) have become obsolete, now that **3a** is produced on a technical scale as a precursor for herbicides.[3] For substituted derivatives, however, e.g., 2,2′,6,6′-tetramethyl-4,4′-bipyridine (**3b**), one still has to rely on a procedure from 1899 (low yields given),[4] which has been somewhat modified in a patent (no yields given).[5]

All practical methods for the preparation of (tetrasubstituted) bipyridines start with the reductive coupling of the respective pyridines, i.e. of **1a**[3] and **1b**[4,5], with sodium to form the tetrahydro-4,4′-bipyridine intermediates **2a** and **2b**.



1 **2** **3** R = CH_3; 49%

1-3	a	b	3	c	d	e	f
R	H	CH_3	R	CO_2H	COCl	COMe	COEt

The crucial final step in all these procedures is the formal abstraction of two hydride ions from **2**. With most of the oxidizing agents tested, pyridines **1** are recovered as the principal products (probably via reversible single electron-transfer), instead of the expected bipyridines **3**. Air oxidation of **2a** affords **3a** in acceptable yields only under "carefully controlled conditions".[6] In our hands only **1b** could be identified when the reduction mixture containing **2b** (*vide infra*) was treated with air. Dehydrogenation of **2b** with *p*-benzoquinone or dibenzoyl

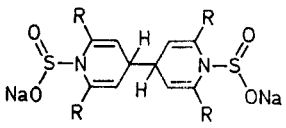
diimide showed no success either, although the *N,N'*-diacetyl derivatives of **2a** are reported to form **3a** in high yield with these reagents.[7]

These difficulties could be overcome when **1b** was reductively dimerized to **2b** in tetrahydrofuran, and the crude **2b** was treated with sulfur dioxide. Thus **3b** was obtained in 49% overall yield.

Sulfur dioxide has occasionally been employed as a dehydrogenating agent for 1,4-dihydropyridines[8] and *N,N'*-dialkyl-4,4'-tetrahydrobipyridines.[9,10] Up to now, one can only speculate on the reaction course. Most probably sulfur dioxide is reduced to sulfoxylic acid[8] either by direct hydride ion transfer from **2b** or through intermediates. The sulfoxylate anion is known to disproportionate into thiosulfate so that the overall reaction may be described by the equation:

$$\mathbf{2b} + 2SO_2 \rightarrow \mathbf{3b} + 2NaHSO_2 \rightarrow Na_2S_2O_3 + H_2O.$$

Intermediate **4** is claimed to be the precursor of the corresponding *N*-sulfonic acid (no physical or analytic data given), obtained by subsequent treatment with hydrogen peroxide.[11]



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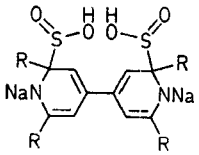

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Dehydrogenation of 1,4-cyclohexadiene to benzene by SO_2 occurs via an ene reaction.[12] If one accepts this reaction as a suitable model for the transformation **2b** → **3b** the intermediate **5** should be taken into account.

In 1898 the tetramethyl compound **3b** had been transformed into the tetracarboxylic acid **3c** with $KMnO_4$ in a very tedious and inefficient reaction.[4] Likewise, a low yield (30%) of 2-carboxy-5-nitropyridine was reported for $KMnO_4$ oxidation of 2-methyl-5-nitropyridine; with CrO_3/H_2SO_4 this carboxylic acid was obtained in 80% yield.[13] Hence the latter method was applied to the case of **3b**, and indeed gave 2,2',6,6'-tetracarboxy-4,4'-bipyridine (**3c**) in 70% yield.

Acid **3c** is a valuable starting material for other 2,2',6,6'-tetrasubstituted 4,4'-bipyridines,[1] e.g., the acid chloride **3d**, and the esters **3e, f**, which were prepared by standard methods.

2,2',6,6'-Tetramethyl-4,4'-bipyridine (3b):

A three-necked round-bottomed flask (100 mL) equipped with gas inlet and septum is charged under nitrogen with a 45% Na dispersion in paraffin (5.0 g, 98 mmol). After treatment with toluene (~ 20 mL) the solvent is removed with a syringe (3 ×) and 2,6-lutidine (5 mL, 4.50 g, 43 mmol) in abs. THF (40 mL) is added. The mixture is stirred magnetically until it solidifies (2–24 h). After standing overnight under nitrogen, SO_2 is passed over the solid mass at such a rate that the solvent does not start to reflux (exothermic reaction!). Cooling with ice may be appropriate. A blue to violet zone is formed on top of the mass, which slowly moves to the bottom of the flask. At this stage introduction of SO_2 is stopped (after 4–6 h), and the flask is cooled with ice/sodium chloride. Then EtOH (50 mL) is added slowly. The mixture is neutralized to pH 7–8 with 12 N NaOH, the organic layer is separated, and

Table. Physical and Spectroscopic Data of Products **3b** and **3c–f**

Product	mp[a] (°C) (solvent)	Molecular Formula[b] or Lit. mp (°C)	IR[c] (KBr) ν(cm^{-1})	UV[d] (MeCN) λ(nm) (lg ε)	^{1}H-NMR[e] (60 MHz; $CDCl_3$/TMS) δ, J(Hz)	^{13}C-NMR[f] (22.6 MHz; $CDCl_3$/TMS) δ
3b	151 (H_2O)	149[4] 152[5]	2920, 1600, 1385, 1380, 1255, 860, 725	239 (4.50); 278 (3.76)	2.58 (s, 12H, CH_3); 7.10 (s, 4H, 4,4'-bipy-H)	24.59 (q, CH_3); 118.08 (d, C-3, 4,4'-bipy); 146.74 (s, C-4, 4,4'-bipy); 158.50 (s, C-2, 4,4'-bipy)
3c	270 (dec) (35% HNO_3)	$C_{14}H_8N_2O_8$ (332.2)	3160, 3080, 1730, 1700, 1600, 1370, 1160, 1080, 990, 910, 780, 760		8.40 (s, 4H, 4,4'-bipy-H)[g]	
3d	205–206 (CH_2Cl_2)	$C_{14}H_4Cl_4N_2O_4$ (405.8)	3080, 1750, 1580, 1265, 1210, 1010, 890, 765	221 (4.16); 271 (sh) (3.74)	8.50 (s, 4,4'-bipy-H)	
3e	248–250 (MeOH)	$C_{18}H_{16}N_2O_8$ (388.3)	3100, 3000, 2980, 1730, 1600, 1540, 1445, 1330, 1275, 1200, 1170, 1140, 1075, 980, 890, 790	221 (4.62); 279 (sh) (3.82)	4.03 (s, 12H, CH_3); 8.50 (s, 4H, 4,4'-bipy-H)	53.44 (q, CH_3); 125.45 (d, C-3, 4,4'-bipy); 146.55 (s, C-4, 4,4'-bipy); 149.83 (s, C-2, 4,4'-bipy); 164.58 (s, CO_2CH_3)
3f	143–145 (EtOH)	$C_{22}H_{24}N_2O_8$ (443.9)	3090, 2990, 1750, 1715, 1590, 1375, 1325, 1255, 1190, 1180, 1150, 1090, 1045, 1015, 865, 790, 785	216 (4.57); 279 (sh) (3.78)	1.50 (t, 12H, J = 8, CH_3); 4.27 (q, 8H, J = 8, CH_2); 8.53 (s, 4H, 4,4'-bipy-H)	13.51 (q, CH_3); 61.58 (t, CH_2); 124.87 (d, C-3, 4,4'-bipy); 145.59 (s, C-4, 4,4'-bipy); 149.15 (s, C-2, 4,4'-bipy); 163.37 (s, CO_2)

[a] Kofler microscope; corrected.
[b] Satisfactory microanalyses obtained: C ±0.3, H ±0.2, N ±0.2.
[c] Recorded on a Perkin-Elmer 157 G spectrophotometer.
[d] Measured using a Perkin-Elmer 330 UV spectrometer.
[e] Obtained on a Varian T 60 spectrometer.
[f] Recorded on a Bruker WH 90 spectrometer.
[g] In DMSO-d_6; signals of the four acid protons not visible.

the aqueous phase is extracted 6–8 times with *t*-BuOMe (20 mL). A yellowish residue is obtained by evaporation of the organic phase. Recrystallization from water gives **3b** as a colorless, crystalline solid; yield: 2.25 g (49%).

2,2',6,6'-Tetracarboxy-4,4'-bipyridine (3c):
Bipyridine **3b** (18.4 g, 86.8 mmol) is dissolved in conc. H_2SO_4 (300 mL). After cooling (0°C) CrO_3 (104 g, 1.04 mol) is added in small portions during 3 h. The mixture is heated to 75°C for 2 h and then poured into a mixture of ice/water (1 L). Tetracarboxylic acid **3c** precipitates as a very fine, colorless powder, which is separated by centrifugation (filtration is difficult). The dried precipitate is recrystallized from 35% HNO_3 to give **3c** as a colorless, microcrystalline compound; yield: 20.1 g (70%).

2,2',6,6'-Tetrachloroformyl-4,4'-bipyridine (3d):
A mixture of **3c** (1.40 g, 4.22 mmol), $SOCl_2$ (6 mL, 9.78 g, 82.3 mmol) and DMF[14] (two drops) is heated under reflux for 4 h. After removal of excess $SOCl_2$ by distillation, the residue is recrystallized from CH_2Cl_2, to give **3d** as colorless crystals; yield: 1.54 g (90%).

2,2',6,6'-Tetramethoxycarbonyl-4,4'-bipyridine (3e):[15]
A mixture of **3c** (3.40 g, 10.2 mmol), abs. MeOH (50 mL), and conc. H_2SO_4 (0.5 mL) is heated under reflux for 4 h. After cooling to room temperature, the product is filtered off and recrystallized from MeOH to give **3e** as colorless crystals; yield: 3.88 g (98%).

2,2',6,6'-Tetraethoxycarbonyl-4,4'-bipyridine (3f):[15]
A mixture of **3c** (1.60 g, 4.82 mmol), abs. EtOH (50 mL), and H_2SO_4 (0.5 mL) is heated under reflux for 2 h. From the clear solution the product crystallizes on cooling to room temperature and, after filtration, is recrystallized from EtOH, giving **3f** as colorless crystals; yield: 2.09 g (96%).

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