A Convenient Synthesis of *cis*-4-(Sulfomethyl)-piperidine-2-carboxylic Acid: NMR Assignment

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cis-4-(Sulfomethyl)piperidine-2-carboxylic acid was obtained in 22% overall yield from 4-(hydroxymethyl)-pyridine *via* the *o*-silyl *N*-oxide and trimethylsilylcyanide. The *cis* configuration of **5** was unambiguously assigned by 200 MHz ^{1}H nmr and cosy experiments.

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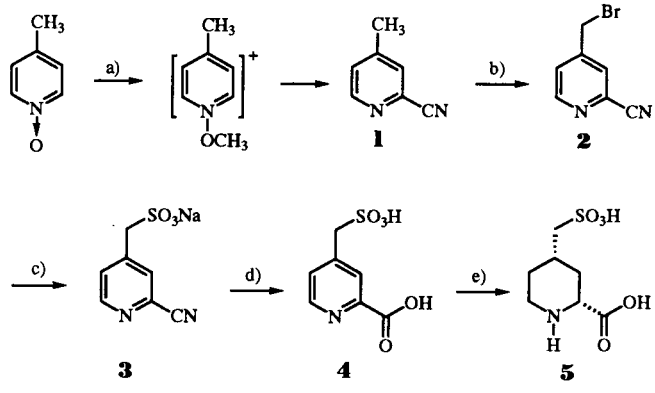
Due to their extraordinary therapeutic potential excitatory amino acids have continued to attract much interest [1,2]. As part of a synthetic program on sulfonic amino acids, a class of compounds yet scarcely studied, we wished to prepare cis-4-(sulfomethyl)piperidine-2-carboxylic acid **5**. This was achieved as outlined in Scheme I.

Methylation of 4-picoline *N*-oxide gave an intermediate salt which was treated without isolation with aqueous potassium cyanide [3]. The use of three equivalents of potassium cyanide increases the yield from 25% to 55%. Alternatively the cyano derivative **1** could also be prepared in a one-pot reaction, although in poor yield (*ca.* 10%) from 4-picoline and tosyl chloride/potassium cyanide. Radical bromination [4] (three equivalents of *N*-bromosuccinimide, benzoyl peroxide) gave a mixture of **2** (29%), starting material (53%), and of gem-dibromo derivative (18%) as de-

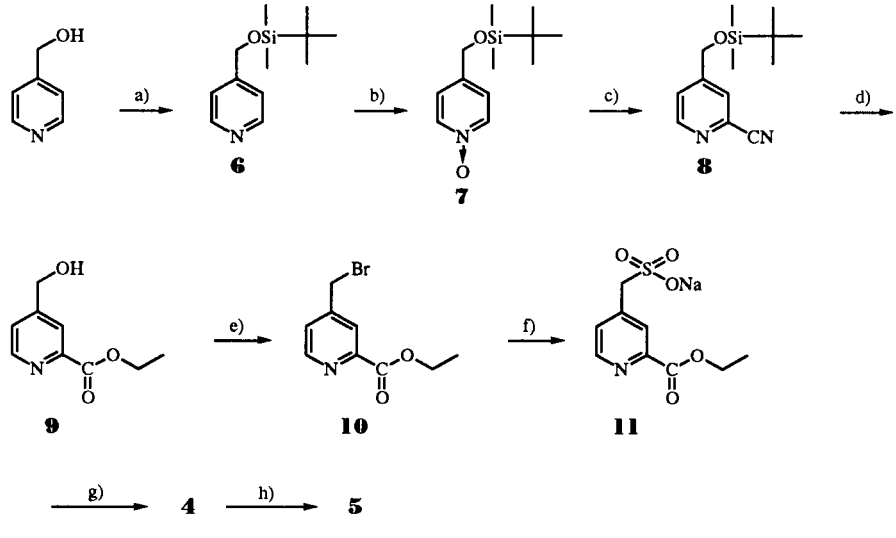
Scheme 1



Reaction conditions:

a) i) $(CH_3)_2SO_4$ ii) KCN/H_2O, b) NBS, $(BzO)_2$ in dry CCl_4, c) Na_2SO_3, H_2O/DMF, d) 6*N* HCl e) H_2/PtO_2 12%, 25°C.

Scheme 2



Reaction conditions:

a) TBDMSiCl, DMF, CH_2Cl_2, b) *m*-CPBA, CH_2Cl_2, 20 h, c) TMSCN, Et_3N, 3 h, d) EtONa, EtOH, 6*N* HCl, e) Ph_3PBr_2, CH_2Cl_2, 25°C, f) Na_2SO_3, DMF/H_2O, g) 6*N* HCl, 24h, h) i) propylene oxide, H_2O. ii) H_2, PtO_2 10%, 12 atm, 25° C.

termined by nmr. Compound **2** could be isolated by silica gel column chromatography, eluting with hexane:ethyl acetate (8:2). Subsequent displacement of the bromine atom by sodium sulfite [5] in aqueous *N,N*-dimethylformamide gave in a nearly quantitative yield the sodium salt **3**. Most of the excess of sodium sulfite and sodium bromide could be eliminated at this stage by precipitation from 95% ethanol. Acidic hydrolysis [6] (6*N*) hydrochloric acid gave 4-(sulfomethyl)pyridine-2-carboxylic acid **4** in 60% yield after recrystallization from water-ethanol (1:4). Catalytic hydrogenation (Platinum oxide, 12 atmospheres, rt) resulted in the expected *cis* derivative **5** (overall yield *ca.* 7%). In order to increase this yield and to allow the preparation of various analogs of **5** a more general route was sought (Scheme II).

4-Pyridylcarbinol was protected with *tert*-butyldimethylsilyl chloride in the presence of imidazole in *N,N*-dimethylformamide [7] at room temperature to give the silyl ether **6** (87%). Oxidation [8] (*m*-Chloroperoxybenzoic acid, methylene chloride) followed by treatment with three equivalents of trimethylsilyl cyanide in triethylamine as described by Fife [9] yields 2-cyanopyridine **8** (overall yield *ca.* 80%). Compound **9** was obtained by esterification and acidic deprotection of **8**. The bromo derivative **10** was prepared satisfactorily by treatment with triphenylphosphine dibromide in methylene chloride. The last steps of the sequence were similar to those of Scheme I. *Cis*-**5** was thus obtained in an overall yield of 22%.

Assignment of the Stereochemistry of **5**.

The stereochemistry of the 2,4-disubstituted compound

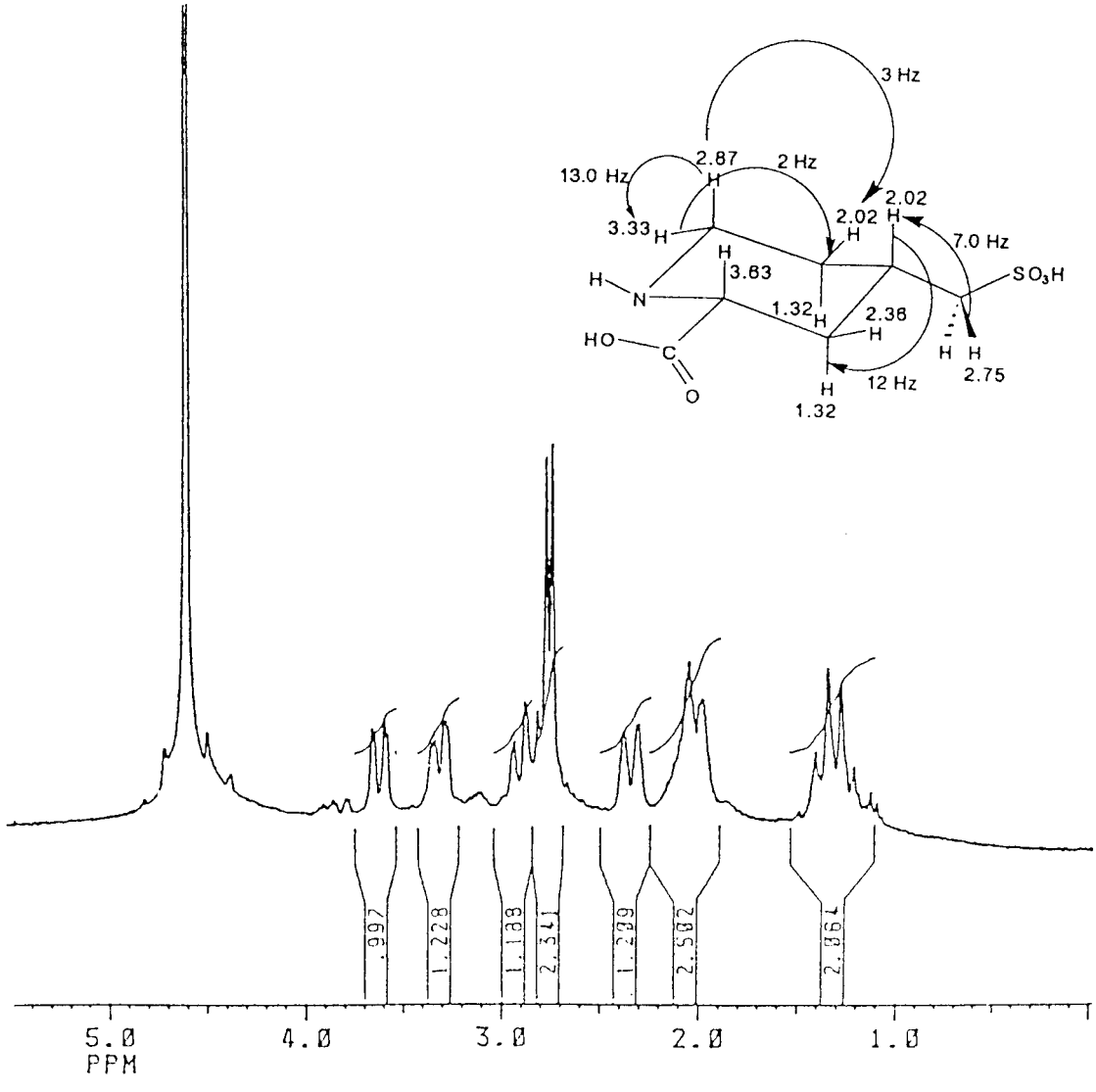


Figure 1. Partial ^{1}H nmr (200 MHz) of *cis*-4-(sulfomethyl)piperidine-2-carboxlic acid 5.

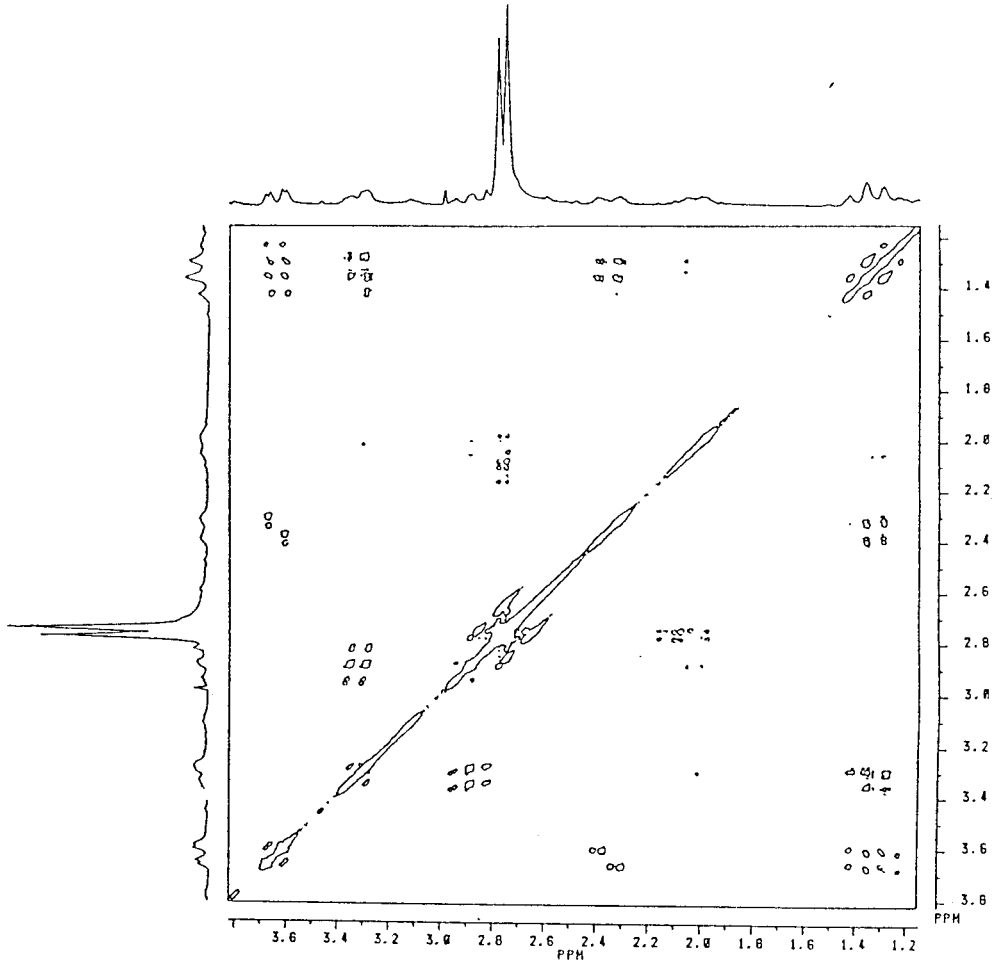


Figure 2. COSY correlations of the hydrogens in 5.

5 was determined by ^{1}H nmr decoupling at 200 MHz and confirmed by COSY experiments (nmr data are given in the experimental).

A Dreiding model of **5** indicates that the molecular adopts the more stable chair-like configuration. This observation is in agreement with the conclusions of Ornstein *et al.* drawn with the CGS 19755 phosphonic analog of **5**. The strongly deshielded H-2 (3.63 ppm) shows a large coupling (*ca.* 12 Hz) and a small coupling (*ca.* 2-3 Hz) to the protons on the C_3 methylene. Assuming the chair-like conformation indicated above for the piperidine ring would require that H-2 has an axial orientation, and CO_2H an equatorial one. The CH_2SO_3H signal was assigned as a doublet at 2.75 ppm with a vicinal coupling constant of 7 Hz. Irradiation experiments allow to attribute unambigously an equatorial position for the methylsulfonic group as indicated in Figure 1. COSY experiments (Figure 2) are in full agreement with ^{1}H nmr assignments.

Conclusion.

In summary the present method allows the ready preparation of piperidine carboxylic acid derivatives bearing a 4-alkylsulfonic side chain. Interestingly a similar methodology is applicable to the preparation of 3-alkylsulfonic derivatives. We have observed that the cyclic amino acids generated by our synthetic procedure were racemic (DL), the CH_2SO_3H and CO_2H group being *cis* to each other, due to the non stereoselective nature of the final hydrogenation step.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H nmr spectra were obtained with a Bruker AC 200 Spectrometer. Mass spectra were obtained with a Kratos MS 30 Spectrometer. The tlc analyses were performed on Merck 60 F254 Silica gel plates. All experiments were carried out with anhydrous solvents under argon atmosphere.

2-Cyano-4-methylpyridine (**1**).

A mixture of 10.9 g (0.1 mole) of 4-methylpyridine *N*-oxide and 12.6 g (0.1 mole) of dimetyl sulfate was heated under reflux for 5 hours. After addition of 20 g of ice, a solution of 21.6 g (0.036 mole) of potassium cyanide in 120 ml of water was added dropwise at -5°. The mixture was kept overnight at 4° and filtered. Recrystallization from *n*-hexane gave pure **1** as a yellow solid, 6.5 g (55%). Using 1 equivalent of potassium cyanide as described led to **1** in 25% yield, mp 87-88°; ir (potassium bromide): 2210 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.43 (s, 3H), 7.33 (dd, 5-H), 7.52 (d, 3-H), 8.56 (d, 6-H); ms: m/z 118 (M^+).

2-Cyano-4-(bromomethyl)pyridine (**2**).

A mixture of 1.2 g (0.01 mole) of 2-cyano-4-methylpyridine, 4.3 g (0.03 mole) of *N*-bromosuccinimide and 0.3 g of benzoyl peroxide in 30 ml of dry carbon tetrachloride was refluxed for 3 hours and allowed to cool to room temperature. The precipitated solid was filtered off and the filtrate was evaporated to dryness. The ^1H nmr on the crude derivative indicated a mixture of starting material (53%) δ: CH_3 = 2.43, monobromo derivative (29%), CH_2Br = 4.4 and dibromo derivative (18%), $CHBr_2$ = 6.6 ppm.

The crude mixture was partially purified by silica gel column chromatography eluting with hexane:ethyl acetate (8:2, v/v) as eluent and was used in the next step without further purification.

2-Cyano-4-(sulfomethyl)pyridine, Sodium Salt (**3**).

A mixture of the above compound **2** (0.3 g, 1.5 mmoles) and sodium sulfite (0.26 g, 2 mmoles) was dissolved in a (9:1, v/v) solution of water-*N*,*N*-dimethylformamide (20 ml). The mixture was concentrated at *ca.* 40° to a nearly dry cake during 12 hours. The residue was digested with ethanol, filtered to remove inorganic salts, and the filtrate was concentrated *in vacuo* to give off white solid; ms: m/z 198 (M^+).

4-(Sulfomethyl)pyridine-2-carboxylic Acid (**4**).

A 250 ml round-bottomed flask was charged with **3** (0.88 g, 4 mmoles), 6*N* hydrochloric acid (50 ml), and the reaction mixture was refluxed for 24 hours. The reaction mixture was concentrated *in vacuo*, and the residue was recrystallized from water-ethanol (2:8, v/v) to give **4** as a white solid. This solid was dissolved in water and treated with three equivalents of propylene oxide for 2 hours at 50° and then concentrated *in vacuo*. Ethanol was added and the solid was filtered and washed with ethanol. The resulting solid was recrystallized from water-ethanol (1:10, v/v) to afford **4** as a white solid 0.52 g (60%); ir (potassium bromide): ν 3000 (OH), 1740 (C=O), 1600 (C=C, C=N), 1200-1150-1050 (SO_3H) cm^{-1}; ^1H nmr (deuterium oxide): δ 4.35 (s, 2H), 7.97 (dd, 5-H), 8.26 (d, 3-H), 8.55 (d, 6-H); ms: m/z 217 (M^+).

cis-4-(Sulfomethyl)piperidine-2-carboxylic Acid (**5**).

A solution of **4** (0.2 g, 0.8 mmole) in water (50 ml) was reacted with hydrogen over platinum oxide (24 mg) at 12 atmospheres in a steel bomb at room temperature for 12 hours. The reaction mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. The residue was purified by passage through Amberlite IR-120. Evaporation of the aqueous column filtrate yielded **5** as a white crystalline solid 0.17 g (85%), mp >260°; ir (potassium bromide): ν 3000 (OH), 1740 (C=O), 1200-1170-1050 (SO_3H) cm^{-1}; ^1H nmr (deuterium oxide): δ 1.32 (m, 2H), 2.02 (m, 2H), 2.36 (dd, 1H, J = 13.0, 3.0 Hz), 2.75 (d, 2H, J = 7.0 Hz), 2.87 (dt, 1H, J = 12.0, 3.0 Hz), 3.33 (dd, 1H, J = 13.0, 2.0 Hz), 3.63 (dd, 1H, J = 12.0, 3.0 Hz); ^{13}C nmr: δ 26.73, 30.48, 31.24, 42.67, 55.30, 57.40, 172.06 (CO_2H); ms: m/z 224 (M^+).

Anal. Calcd. for $C_7H_{17}NO_7S$ (M + $2H_2O$): C, 32.43; H, 6.61; N, 5.40; S, 12.37. Found: C, 32.14; H, 6.37; N, 5.10; S, 12.24.

4-[{(*tert*-Butyldimethylsilyl)oxy}methyl]pyridine (**6**).

A mixture of 4-(hydroxymethyl)pyridine (8.5 g, 78 mmoles), *tert*-butyldimethylsilyl chloride (13 g, 86 mmoles) and imidazole (6.4 g, 96 mmoles) in 100 ml of dry dimethylformamide/methylene chloride (9:1, v/v) was stirred for 3 hours. The solution was evaporated *in vacuo*, and water was added. Extraction with ethyl acetate-hexane (1:1, v/v) yielded ether **6** as an oil 15.52 g (87%); ^1H nmr (deuteriochloroform): δ 0.12 (s, 6H), 0.93 (s, 9H), 4.75 (s, 2H), 7.36 (d, 2H), 8.42 (d, 2H).

4-[{(*tert*-Butyldimethylsilyl)oxy}methyl]pyridine *N*-Oxide (**7**).

The above pyridyl ether **6** (15.22 g, 68 mmoles) was dissolved in dry methylene chloride (200 ml), *m*-chloroperoxybenzoic acid (15.5 g, 90 mmoles) was added and the mixture was stirred at room temperature for 20 hours. The reaction mixture was washed with aqueous 1*N* sodium hydroxide. The organic phase was dried (sodium sulfate) and evaporated to give **7** (15.33 g, 94%) as a white solid which was used without further purification; ir (potassium bromide): ν 1170 (N^+-O^-) cm^{-1}.

2-Cyano-4-[{(*tert*-butyldimethylsilyl)oxy}methyl]pyridine (**8**).

A mixture of *N*-oxide **7** (15 g, 62.6 mmoles), anhydrous triethylamine (20 ml) and trimethylsilyl cyanide (24 ml, 180 mmoles) was heated at 90° for 3 hours. The solution was evaporated *in vacuo*, the residue was poured into water and extracted with ethyl acetate (3 x 50 ml). The combined organic solution was dried over anhydrous sodium sulfate, filtered, and the filtrate was evaporated *in vacuo*. The residue was purified on a silica gel column and eluted with ethyl acetate:hexane (1:9, v/v) to give **8** as a yellow oil 13 g (83%); ir: ν 2220 (CN), 1600 (C=C, C=N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.12 (s, 6H), 0.93 (s, 9H), 4.77 (s, 2H), 7.45 (dd, 5-H), 7.66 (s, 3-H), 8.63 (d, 6-H).

Ethyl 4-(Hydroxymethyl)pyridine-2-carboxylate (**9**).

To a solution of **8** (9.6 g, 38.4 mmoles) in anhydrous ethanol (120 ml) was added a solution of sodium ethoxide prepared from 0.144 g (62 mg-atoms) of sodium in ethanol (3.6 ml). After 20 hours at room temperature the solution was cooled in an ice-bath and a solution of 6*N* hydrochloric acid (15.6 ml) was added dropwise. After 20 hours at room temperature 6*N* sodium hydroxide (15.6 ml) was added and the solution was evaporated *in vacuo*. The residue was diluted with water and extracted with methylene chloride (3 x 30 ml). The combined organic layer was dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo*. The oily residue was induced to crystallize by triturating with ether-hexane (1:5, v/v) to give **9** as a slightly colored solid 6 g (86%); ir (potassium bromide): ν 3500-3000 (OH), 1720 (C=O), 1600 (C=C, C=N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.40 (t, 3H), 3.46 (s, 1H), 4.42 (q, 2H), 4.81 (s, 2H), 7.48 (d, 5-H), 8.08 (s, 3-H), 8.61 (d, 6-H).

Ethyl 4-(Bromomethyl)pyridine-2-carboxylate (**10**).

Triphenylphosphine dibromide was generated from triphenylphosphine (0.8 g, 3.1 mmoles) and 0.16 ml (0.49 g, 3.1 mmoles) of bromine in methylene chloride (10 ml) at 0°. A solution of **9** (0.46 g, 2.55 mmoles) in methylene chloride (5 ml) was added dropwise to the suspension of triphenyl phosphine dibromide in methylene chloride. After 0.5 hour at room temperature the solution was

washed three times with water, the organic layer was dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo*. The residue was purified on a silica gel column and eluted with ethyl acetate:hexane (1:1, v/v) to give **10** as an orange oil 0.5 g (80%); ir: ν 2950, 1720 (C=O), 1600 (C=C, C=N) cm^{-1}.

Ethyl 4-(Sulfomethyl)pyridine-2-carboxylate, Sodium Salt (**11**).

A mixture of **10** (0.5 g, 2 mmoles) and sodium sulfite (0.6 g, 4.76 mmoles) in 30 ml of *N,N*-dimethylformamide/water (1:9, v/v) was heated at 40° overnight. Evaporation of the solution *in vacuo* gave a crude residue. The residue was digested with ethanol, filtered to remove inorganic salts, and the filtrate was concentrated *in vacuo* to give **11** as a white solid 0.43 g (80%); ir (potassium bromide): ν 1720 (C=O), 1600 (C=C, C=N), 1210-1120-1050 (SO_3H) cm^{-1}.

4-(Sulfomethyl)pyridine-2-carboxylic Acid (**4**).

A mixture of **11** (0.4 g, 1.5 mmoles) in 6*N* hydrochloric acid (25 ml) was refluxed for 24 hours. The reaction mixture was concentrated *in vacuo* and the residue was recrystallized from water-ethanol (2:8, v/v) to give **4** (0.27 g). This solid was dissolved in water and treated with three equivalents of propylene oxide for 2 hours at 50° and then concentrated *in vacuo*. Ethanol was added and the solid was filtered and washed with ethanol. The resulting solid was recrystallized from water-ethanol (1:10, v/v) to afford **4** as a white solid 0.22 g (70%).

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