Free-Radical Approach to 4-Substituted Dipicolinates

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Keywords: Heterocycles / Acylation / Alkylation / Radical reactions

Dimethyl pyridine-2,6-dicarboxylate was selectively substituted through free-radical reactions. The substitution involves the generation of free radicals through Fenton-type reactions, followed by hydrogen abstraction from aldehydes or alcohols. The resultant carbon-centered acyl, alkyl, or hydroxyalkyl free radicals regioselectively attack protonated dimethyl pyridine-2,6-dicarboxylate at position 4, yielding the corresponding dimethyl 4-acyl-, 4-alkyl-, and 4-(hydroxyalkyl)pyridine-2,6-dicarboxylates.

Introduction

Pyridine-2,6-dicarboxylic (dipicolinic) acid and its derivatives are highly useful tridentate ligands. Pyridine-2,6-dicarboxylic acid forms nine-coordinating luminescent complexes with lanthanides, providing high quantum yields of phosphorescence[1] and used as luminescent tags, labels, and barcodes.[2] Chiral pybox (2,6-bis-oxazolidinopyridine) ligands, which can be easily prepared from esters or the chloroanhydride of pyridine-2,6-dicarboxylic acid through the use of commercially available chiral amino alcohols, have found numerous applications in transition metal-catalyzed asymmetric syntheses.[3]

Despite the simplicity of the preparation of tridentate ligands based on pyridine-2,6-dicarboxylic acid, fabrication of complex systems based on its derivatives, such as concave pyridines,[4] peptide-incorporated metal chelators,[5] inhibitors of farnesyltransferase,[6] luminescent probes,[7] or polymer-bound pybox ligands,[8] necessitates derivatization of the pyridine ring. Consequently, substantial efforts have been concentrated on the preparation of functionalized pyridine-2,6-dicarboxylic acid derivatives. Instead of the cheap and abundant pyridine-2,6-dicarboxylic acid, however, these syntheses have had to be based on 4-halo-pyridine-2,6-dicarboxylates, prepared from expensive chelidamic acid (4-oxo-1,4-dihydro-2,6-pyridine dicarboxylic acid).[9] Existing methods of preparation of 4-heteroatom-functionalized pyridine-2,6-dicarboxylic acid derivatives involve the replacement of the 4-halogen atom with different *N*- and *O*-nucleophiles.[10] Replacement of the 4-halogen atom with carbon-based substituents has been achieved through palladium-catalyzed couplings with vinyltributyltin,[8] Sonogashira coupling,[4,11] Suzuki coupling,[6] the Heck reaction,[5] or reactions with stabilized enolates.[12]

Direct functionalization of pyridine-2,6-dicarboxylates could be an attractive alternative to these syntheses based on chelidamic acid. Such a functionalization cannot be performed by conventional substitution reactions, however, because of the resistance of the pyridine ring in pyridine-2,6-dicarboxylic acid derivatives to electrophilic and nucleophilic attacks.

Free radical substitutions in aromatic systems have been known for a long time but are relatively rarely used in preparative synthesis.[13] The regioselectivity of free-radical substitution in monosubstituted benzenes is generally low, although strong –*E* substituents, such as cyano, ester, and nitro groups, direct the substitution to the *ortho* and *para* positions.[14]

Minisci and co-authors were first to discover that free-radical substitution with nucleophilic carbon-centered radicals in protonated pyridine and quinoline systems proceeds regioselectively with almost exclusive substitution at positions 2 and 4.[15] Treatment of organic peroxides with Fe^{II}[16] and Ti^{III}[17] reagents, followed by hydrogen or iodine transfer, as well as oxidative silver-catalyzed decarboxylations,[18] were used for the generation of the carbon-centered free radicals. The Minisci reaction was also successfully extended to other nitrogen-containing heteroarenes. The presence of electron-withdrawing substituents in heteroaromatic rings was reported to increase the substitution rates substantially,[19] making the Minisci reaction potentially suitable for functionalization of electron-poor system such as pyridine-2,6-dicarboxylic acid derivatives.

Minisci's methodology, in contrast to the more commonly used tributyltin-mediated reductive free-radical reactions,[20] requires at least equimolecular quantities of hydrogen or alkyl peroxide. However, the generation of free radicals through Fenton-type reactions relies on cheap and en-

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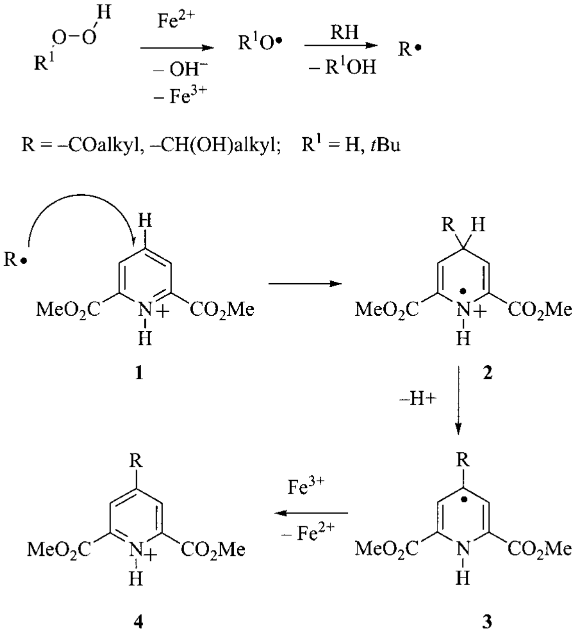
DOI: 10.1002/ejoc.200400637

vironmentally friendly reagents, making them more suitable for large-scale syntheses.

In this paper we report on the derivatization of pyridine-2,6-dicarboxylic acid derivatives through free radical substitution reactions that were found to proceed differently from literature examples. These reactions produce various 4-carbon-substituted derivatives that may be useful precursors for the preparation of complex 4-functionalized pyridine-2,6-dicarboxylic acid- and pybox-type ligands.

Results and Discussion

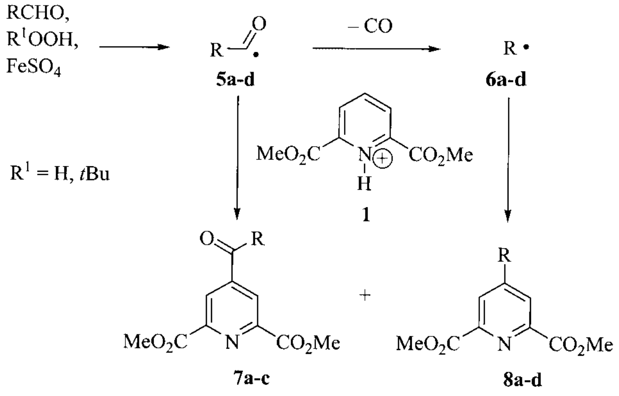
Our approach to free-radical derivatization of pyridine-2,6-dicarboxylates (Scheme 1) involved the generation of oxygen-centered radicals through Fenton-type reactions, followed by abstraction of a hydrogen atom from aldehydes and alcohols by the produced oxygen-centered radicals. The resulting nucleophilic carbon-centered radicals were expected, analogously to reports by Minisci,[21] to attack protonated dimethyl dipicolinate (**1**). Subsequent in situ *C*-deprotonation of resultant cation-radicals **2** and oxidation of the intermediate radicals **3** with Fe^{3+} were intended to yield 4-substituted dipicolinate derivatives of type **4**.



Scheme 1.

Our initial attempts to perform the derivatization of dimethyl pyridine-2,6-dicarboxylate were carried out in aqueous solutions acidified with 1–5 equiv. of sulfuric acid, with use of the $H_2O_2/FeSO_4$ system for generation of hydroxy radicals and aliphatic aldehydes as hydrogen donors. None of these attempts produced any substitution product, resulting in complete recovery of the starting material. These results were unexpected, as literature data[19] report enhanced reactivity of acyl-substituted azaaromatic compounds toward free-radical attacks. The observed very low reactivity of pyridine-2,6-dicarboxylic system can be interpreted, however, by taking account of the low basicity of pyridine-2,6-dicarboxylates,[22] which results in very low equilibrium concentrations of the corresponding cations **1** in the reaction mixture.

Performing the reaction in 30% water/H_2SO_4 as solvent (Scheme 2, procedure A) provided the necessary highly acidic conditions to enforce the protonation of dimethyl pyridine-2,6-dicarboxylate, and the designed free-radical substitutions then indeed took place. These reactions proceeded with complete regioselectivity and no detectable amounts of isomeric products were observed, despite the presence of two electron-withdrawing methoxycarbonyl groups, known to favor 3-substitution.[14,23]



Recovery-based isolated yields

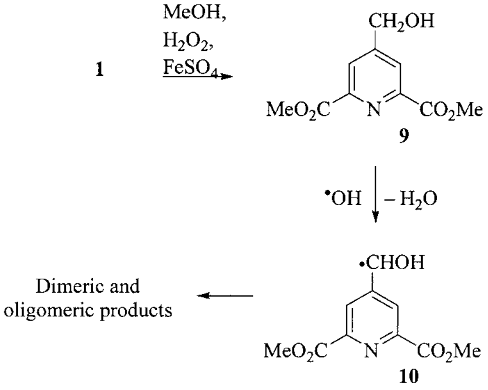
Procedure A		7	8
a	R = Et	< 2%	57%
b	R = Me	< 2%	< 2%
c	R = Ph	< 2%	< 2%
d	R = *i*Pr	< 2%	76%
Procedure B[22]			
a	R = Et	43%	12%
b	R = Me	68%	< 2%
c	R = Ph	41%	< 2%

Scheme 2.

Instead of the expected ketones of type **7**, however, the only isolated reaction products were 4-alkyl derivatives of type **8**. The formation of these products can be explained by the decarbonylation of the initially formed acyl radicals of type **5**, followed by the free radical attack of the resultant alkyl radicals of type **6** on the protonated dipicolinate **1**. Decarbonylation in free radical substitutions had previously been reported in similar reactions of heteroaromatic substitution only for acyl radicals possessing quaternary – but not tertiary or secondary – α-carbon atoms,[24] and even in this case the percentage of the decarbonylated product was very small. It could be assumed that despite the applied highly acidic reaction media, the concentration of the protonated form of dimethyl pyridine-2,6-dicarboxylate still remained low, thus decreasing the bimolecular free-radical addition rates. As a result, the competing intramolecular decarbonylation pathway prevailed, resulting in the formation of alkyl radicals of type **6** and eventually in the formation of 4-alkyl derivatives **8a** and **8d**. No measurable amounts of substitution products **7/8b** or **7/8c** were observed in reactions with benzaldehyde and acetaldehyde under these reaction conditions, which is probably related to very low decarbonylation rates of acyl radicals **5b** and **5c**.[25]

The chemoselectivity of the reaction can be changed by further increasing the acidity of the reaction media. Because of the low solubility of $FeSO_4$ in acetic acid, procedure B provided less than 100% conversions (no optimization of the reaction conditions was carried out).[26] Treatment of dimethyl pyridine-2,6-dicarboxylate with aliphatic and aromatic aldehydes in a mixture of acetic acid and 66% sulfuric acid as solvent and with a tBuOOH/$FeSO_4$ system for the generation of radicals (procedure B) produced an outcome substantially different to that of procedure A. Instead of the 4-ethylpyridine **8a**, the predominant reaction product was the 4-propionylpyridine **7a**. The same free-radical acylation also proceeded successfully with benzaldehyde and acetaldehyde, both of which had failed to provide any substitution products in procedure A.

Free-radical reactions were also used for direct introduction of 4-hydroxyalkyl substituents. Treatment of dimethyl pyridine-2,6-dicarboxylate with slowly added aqueous solutions of $FeSO_4$ and H_2O_2 in aqueous methanol produced the 4-hydroxymethyl-substituted pyridine **9** (Scheme 3) in 30% yield (48% recovery-based). The reaction mechanism involves hydrogen transfer from methanol to initially formed hydroxy radicals, followed by the free-radical attack of the resultant nucleophilic hydroxymethyl radicals on the protonated pyridine **1**, as shown in Scheme 1. Subsequent in situ deprotonation and oxidation of the intermediate radical of type **3** (R = CH_2OH) with Fe^{3+} produced the 4-hydroxymethyl-substituted pyridine **9**.

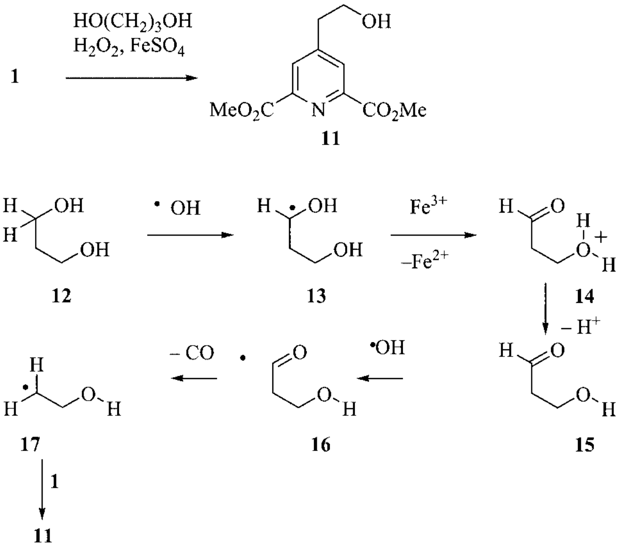


Scheme 3.

Acceptable yields of the 4-hydroxymethyl-substituted pyridine **9** could be obtained only below 50% conversions. Attempts to achieve 100% conversion provided lower yields of **9**, accompanied by unidentified polymeric byproducts. The formation of polymeric products can be expected by taking account of the ability of alcohol **9** to undergo hydrogen abstraction with hydroxy radicals. Such a reaction should produce a highly stabilized and nucleophilic α-hydroxybenzylic radical **10**, which could undergo further transformation to produce a number of oligomeric products.[27]

Although chromatographic separation of the reaction product **9** from the starting dimethyl pyridine-2,6-dicarboxylate is straightforward, it may give rise to practical problems at multigram scales. To bypass chromatographic separation, an alternative purification procedure involving silylation of the crude reaction mixture was elaborated. Preparation of other functionalized pyridine-2,6-dicarboxylates from alcohol **9** can easily be done through its conversion into 4-iodomethyl and 4-formylpyridine-2,6-dicarboxylates by existing methodologies.

Similar free radical reactions with alcohols such as ethanol, butanol, butane-1,4-diol, and 3-acetoxypropanol failed to provide any appreciable yields of monomeric substitution products. This could have been expected, as the free radical substitution competes with the oxidation of α-hydroxyalkyl radicals by Fe^{3+}. The oxidation rates for reactions with aliphatic alcohols are substantially larger than that for methanol. This oxidation is the most probable reason for unexpected results in an analogous $FeSO_4$/H_2O_2-initiated reaction between dimethyl pyridine-2,6-dicarboxylate and an excess of propane-1,3-diol, as the major isolable reaction product was found to be the 2-hydroxyethyl pyridine **11** (Scheme 4).



Scheme 4.

Most probably, the mechanism of formation of the hydroxyethyl-substituted pyridine **11** includes an attack of the 2-hydroxyethyl radical **17** on the protonated ester **1**. A possible reaction mechanism for the formation of the 2-hydroxyethyl pyridine **11** could involve hydrogen abstraction from propane-1,3-diol by Fenton-generated hydroxy radicals. Subsequent oxidation of the resultant radical **13** with Fe^{3+} cations[21] should provide 3-hydroxypropanal **14**, which should be capable of undergoing a second hydrogen transfer followed by decarbonylation, in analogy to the reactions shown in Scheme 2. Because neither butanol nor 3-acetoxypropanol provide free-radical substitution products under similar reaction conditions, the second hydroxy group clearly participates in this process.

In conclusion, we have demonstrated a new, one-step approach for the regiospecific preparation of 4-alkyl- and 4-acylpyridine-2,6-dicarboxylates by free-radical methodology involving the generation of oxygen-centered radicals through Fenton-type reactions, abstraction of hydrogen from aromatic and aliphatic aldehydes, and free-radical substitution of protonated dimethyl pyridine-2,6-dicarboxylate by the resultant acyl radicals. The substitution can be carried out in highly acidic solution and is accompanied by complete or partial decarbonylation of acyl radicals. The decarbonylation can be controlled by changing the acidity of reaction media. The same methodology was also used for the preparation of 4-(hydroxymethyl)- and 4-(2-hydroxyethyl)pyridine-2,6-dicarboxylates by use of methanol and propane-1,3-diol for the generation of carbon-centered radicals.

Experimental Section

All reagents were commercial C.P. grade and were not additionally purified unless otherwise stated. Dimethyl pyridine-2,6-dicarboxylate was synthesized from pyridine-2,6-dicarboxylic acid by the published procedure. *tert*-Butyl hydroperoxide contained 20% of di-*tert*-butyl peroxide. Dropwise addition was carried out with a syringe pump. Flash chromatography was performed on 230–400 mesh Silica gel 60 supplied by Merck. Elementary microanalyses were performed in the Laboratory of Microanalysis of the Hebrew University. Electrospray mass spectra of compounds were recorded on a Finnegan LCQ Classic mass spectrometer in dichloromethane solutions in the presence of 5% of $MeSO_3H$. ^{1}H NMR spectra were recorded in $CDCl_3$ on Bruker AMX 300 and DRX 400 NMR spectrometers. Chemical shifts (δ) are measured in ppm using residual solvent peak for calibration.

General Procedure A, for Preparation of Dimethyl 4-Alkylpyridine-2,6-dicarboxylates 8a and 8d: Aqueous solutions of $FeSO_4$ (1 mmol) and H_2O_2 (30% aqueous solution, 5 mmol) were added dropwise over 15 min at 0 °C with vigorous stirring to a mixture of dimethyl pyridine-2,6-dicarboxylate (0.49 g, 2.5 mmol), an aldehyde (7.5 mmol), and H_2SO_4 (30% aqueous solution, 15 mL). The reaction mixture was stirred for 15 min at 0 °C, treated with saturated aq. K_2CO_3 to pH 2, and extracted with ethyl acetate. Combined extracts were dried and evaporated, and the residue was purified by flash chromatography to give compounds **8a** and **8d**.

Dimethyl 4-Ethylpyridine-2,6-dicarboxylate (8a): This compound was prepared from dimethyl pyridine-2,6-dicarboxylate (0.49 g) and propionic aldehyde (0.44 g) Chromatography with hexane/ethyl acetate (7:3 to 1:1) provided the title compound (0.32 g, 57%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.29 (t, J = 7.5 Hz, 3H), 2.82 (q, J = 7.5 Hz, 2 H), 4.02 (s, 6 H), 8.16 ppm (s, 2 H). ^{13}C NMR (75 MHz): δ = 13.8, 27.9, 52.9, 127.5, 147.9, 155.9, 165.1 ppm. IR (film): $\tilde{\nu}$ = 646, 908, 1217, 1253, 1363, 1444, 1728 cm^{-1}. MH^{+} 224.1 calcd. 224.1. $C_{11}H_{13}NO_4$ (223.23): found: C 58.96, H 5.87, N 6.44; calcd. C 59.18, H 5.83, N 6.30.

Dimethyl 4-Isopropylpyridine-2,6-dicarboxylate (8d): This compound was prepared from dimethyl pyridine-2,6-dicarboxylate (0.49 g) and isobutyric aldehyde (0.54 g) Chromatography with hexane/ethyl acetate (7:3 to 1:1) provided the title compound (0.40 g, 76%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (d, J = 6.9 Hz, 6 H), 3.07 (sept., J = 7 Hz, 1 H), 4.02 (s, 6 H), 8.18 ppm (s, 2 H). IR (film): $\tilde{\nu}$ = 646, 908, 1217, 1250, 1266, 1332, 1360, 1443, 1717 cm^{-1}. MH^{+} 238.1 calcd. 238.1. $C_{12}H_{15}NO_4$ (237.25): found: C 60.63, H 6.27, N 5.83; calcd.: C 60.75, H 6.37, N 5.90.

General Procedure B, for Preparation of Dimethyl 4-Acylpyridine-2,6-dicarboxylates 7a–c: A solution of *t*BuOOH (4.50 g, 50 mmol) in acetic acid (3 mL) was added dropwise over 5 min with vigorous stirring to a solution of dimethyl pyridine-2,6-dicarboxylate (4.88 g, 25 mmol) in a mixture of acetic acid (6 mL), water (2 mL), conc. sulfuric acid (4 mL), $FeSO_4{\cdot}7H_2O$ (6.95 g, 25 mmol), and an aldehyde (50 mmol). The reaction mixture was stirred for an additional 2 min, poured into water, and extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried, and evaporated, and the residue was separated by flash chromatography to yield compounds **7a**–**c** along with starting dimethyl pyridine-2,6-dicarboxylate, and (for **7a**) minor amounts of 4-ethylpyridine **8a**.

Dimethyl 4-Propionylpyridine-2,6-dicarboxylate (7a): This compound was prepared from dimethyl pyridine-2,6-dicarboxylate (0.39 g) and propanal (0.23 g). Chromatography with hexane/ethyl acetate (7:3 to 1:1) provided the title compound (0.17 g, 34%), along with recovered dimethyl pyridine-2,6-dicarboxylate (85 mg, 22%) and **8a** (54 mg, 12%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, J = 7.1 Hz, 3 H), 3.09 (q, J = 7.1 Hz, 2 H), 4.04 (s, 6 H), 8.69 ppm (s, 2 H). ^{13}C NMR (75 MHz): δ = 7.5, 32.6, 53.4, 125.4, 145.3, 149.5, 164.5, 198.1 ppm. IR (film): $\tilde{\nu}$ = 774, 999, 1152, 1212, 1246, 1437, 1697, 1749 cm^{-1}. MH^{+} 252.1 calcd. 252.1. $C_{12}H_{13}NO_5$ (251.24): found: C 56.97, H 5.19, N 5.29; calcd.: C 57.37, H 5.22, N 5.58.

Dimethyl 4-Acetylpyridine-2,6-dicarboxylate (7b): This compound was prepared from dimethyl pyridine-2,6-dicarboxylate (0.39 g) and acetaldehyde (0.18 g). Chromatography with hexane/ethyl acetate (7:3 to 1:1) provided the title compound (0.25 g, 52%), along with recovered dimethyl pyridine-2,6-dicarboxylate (0.10 g, 26%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.73 (s, 3 H), 4.06 (s, 6 H), 8.70 ppm (s, 2 H). ^{13}C NMR (75 MHz): δ = 26.8, 53.3, 53.2, 125.4, 145.2, 149.5, 164.8, 198.2 ppm. IR (film): $\tilde{\nu}$ = 997, 1145, 1165, 1245, 1332, 1436, 1699, 1749 cm^{-1}. MH^{+} 238.1 calcd. 238.1. $C_{11}H_{11}NO_5$ (237.21): found: C 55.70, H 4.67, N 5.90; calcd.: C 55.70, H 4.65, N 5.68.

Dimethyl 4-Benzoylpyridine-2,6-dicarboxylate (7c): This compound was prepared from dimethyl pyridine-2,6-dicarboxylate (4.88 g) and benzaldehyde (5.3 g). Chromatography with toluene/ethyl acetate 3:1 provided title compound (2.18 g, 29%) along with recovered dimethyl pyridine-2,6-dicarboxylate (1.46 g, 30%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.02 (s, 6 H), 7.52 (t, J = 7.6 Hz, 2 H), 7.66 (t, J = 7.3 Hz, 1 H), 7.78 (d, J = 7.3 Hz, 2 H), 8.52 ppm (s, 2 H). ^{13}C NMR (75 MHz): δ = 53.3, 127.0, 128.9, 130.0, 134.9, 147.2, 148.9, 164.4, 193.1 ppm. IR (film): $\tilde{\nu}$ = 700, 1255, 1279, 1440, 1669, 1724 cm^{-1}. MH^{+} 300.1 calcd. 300.1. $C_{18}H_{13}NO_5$ (299.28): found: C 64.15, H 4.41, N 4.61; calcd.: C 64.21, H 4.35, N 4.68.

Dimethyl 4-(Hydroxymethyl)pyridine-2,6-dicarboxylate (9): Aqueous solutions of $FeSO_4{\cdot}7H_2O$ (14.4 g, 52 mmol) and H_2O_2 (30% solution, 40 mL, 0.35 mol) were added dropwise over 1 h to a mixture of dimethyl pyridine-2,6-dicarboxylate (10.2 g, 52 mmol), methanol (30 mL), and H_2SO_4 (30% aqueous solution, 70 mL). The reaction mixture was stirred for an additional 15 min, treated with saturated aq. K_2CO_3 to pH 2, and extracted with ethyl acetate. The combined extracts were dried and evaporated, and the residue was separated by flash chromatography to yield a mixture of the title compound **9** and unreacted dimethyl pyridine-2,6-dicarboxylate.

For large scales the resultant mixture was separated by the following procedure. Chlorotrimethylsilane (9.0 mL, 71 mmol) and hexamethyldisilazane (15 mL, 71 mmol) were added to a solution of the reaction mixture in CH_2Cl_2 (120 mL). The reaction mixture was stirred for 70 min at room temperature, the precipitate of starting dimethyl pyridine-2,6-dicarboxylate was filtered off, and the filtrate was evaporated. The residue was diluted in 40 mL of a 2:1 mixture of ether and petroleum ether and washed with water. The aqueous solution was extracted with diethyl ether, the combined organic solutions were evaporated, and the residue was dissolved in a mixture of MeOH (10 mL) and aqueous HCl (10%, 10 mL). After 16 h the resultant residue of title compound **9** was filtered (2.85 g, 24%).

^1H NMR (300 MHz, $CDCl_3$, after exchange of OH proton with D_2O): $\delta = 4.02$ (s, 6 H), 4.89 (d, $J = 5.4$ Hz, 2 H), 8.31 ppm (s, 2 H). ^{13}C NMR (75 MHz): $\delta = 53.2$, 62.8, 125.3, 148.2, 153.5, 165.1 ppm. IR (film): $\tilde{\nu} = 784$, 909, 1227, 1369, 1452, 1699, 1722, 3486 cm^{-1}. MH^+ 226.1 calcd. 226.1. $C_{10}H_{11}NO_5$ (225.20): found: C 53.08, H 5.19, N 6.05; calcd.: C 53.33, H 4.89, N 6.22. Chromatographic separation with hexane/ethyl acetate (7:3 to 1:2) in an identical experiment provided a 30% yield of the title compound and 38% recovery of starting material.

Dimethyl 4-(2-Hydroxyethyl)pyridine-2,6-dicarboxylate (11): Solutions of $FeSO_4 \cdot 7H_2O$ (4.17 g, 15 mmol) and H_2O_2 (30% aqueous solution, 12 mL, 105 mmol) were added dropwise to a mixture of dimethyl pyridine-2,6-dicarboxylate (2.93 g, 15 mmol), propane-1,3-diol (13 mL, 180 mmol), and H_2SO_4 (30% aqueous solution, 20 mL). The reaction mixture was stirred for 15 min after completion of the addition, treated with saturated aq. K_2CO_3 to pH 2, and extracted with ethyl acetate. The combined extracts were dried and evaporated, and the residue was purified by flash chromatography (hexane/ethyl acetate, 7:3 to 1:2) to yield the title compound **11** (1.29 g, 32%) and recovered starting material (25%). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.02$ (t, $J = 6.2$ Hz, 2 H), 4.00 (t, $J = 6.2$ Hz, 2 H), 4.04 (s, 6 H), 8.23 ppm (s, 2 H). ^{13}C NMR (75 MHz): $\delta = 38.0$, 53.0, 61.6, 128.7, 147.8, 151.6, 165.1 ppm. IR (film): 734, 909, 1218, 1253, 1363, 1445, 1604, 1729, 2955, 3450 cm^{-1} (br). MH^+ (electrospray in the presence of $MeSO_3H$): 240.3. $C_{11}H_{13}NO_5$ (239.22): found: C 55.25, H 5.48, N 5.80; calcd.: C 55.23, H 5.48, N 5.86.

Acknowledgments

This research was supported by the Israel Science Foundation (Grant No. 176/02-1).

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Received: September 7, 2004