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Synthesis of the Deuterated Compounds Diethyl-4-D-pyridine-2,6-dicarboxylate and Diethyl-3,4,5-D_3-pyridine-2,6-dicarboxylate by Catalytic Reductive Debromination

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Summary

The synthesis of the mono- and trideutero compounds diethyl-4-D-pyridine-2,6-dicarboxylate (**4**) and diethyl-3,4,5-D_3-pyridine-2,6-dicarboxylate (**5**) was achieved under a deuterium gas atmosphere by reductive debromination of diethyl-4-bromopyridine-2,6-dicarboxylate (**1**) and diethyl-3,4,5-tribromopyridine-2,6-dicarboxylate (**2**), respectively, using palladium black as catalyst and dichloromethane as solvent. The deuterium incorporation at the specified positions exceeded 95%.

Key Words: diethyl-4-D-pyridine-2,6-dicarboxylate, diethyl-3,4,5-D_3-pyridine-2,6-dicarboxylate, reductive debromination

Introduction

Recently one of us became interested in the coordination chemistry of 2,11-diaza-(2,6)[3.3]pyridinophane and their derivatives.[1] In order to assign the NMR signals of the resulting paramagnetic complexes, the preparation of partially deuterated tetraazamacrocycles was required. Within the synthesis of the macrocyclic ligands, 2,6-bis(chloromethyl)pyridine is an important precursor, which is itself eventually prepared from diethyl-pyridine-2,6-dicarboxylate via the intermediate pyridine-2,6-dimethanol.[2] Here we report on the synthetic procedures of the mono- and trideutero compounds **4** and **5**.

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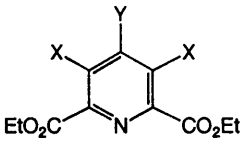
For the introduction of deuterium into a pyridine ring, several procedures have been described.[3,4,5] Because of the reported relative ease of catalytic substitution of halogen atoms at the pyridine moiety by hydrogen atoms using dihydrogen gas,[6,7] we decided to follow an analogous procedure in our efforts to synthesize the deuterated ligands.



1 : X = H; Y = Br
2 : X = Y = Br
3 : X = Y = H
4 : X = H; Y = D
5 : X = Y = D

Results and Discussion

The starting points of our deuteration experiments are the mono- and tribromo derivatives **1** and **2** of diethyl-pyridine-2,6-dicarboxylate, which were obtained from commercially available chelidamic acid according to the synthetic routes reported by Takalo and Kankare[8] and by Dohrn and Diedrich[9].

In order to determine the best reaction conditions for the catalytic debromination of compounds **1** and **2**, trial reductions were carried out in dichloromethane solutions at room temperature under low pressures of hydrogen gas (0.2–0-4 bar excess pressure of H_2). The type of palladium catalyst employed in the reaction proved to be of crucial importance. Thus, no reaction was observed when using the palladium catalyst in its oxidic form (Pd-C, 5% and 10%), while the catalyst displayed a high activity in its reduced form (palladium black).[10] In addition, operating temperatures were crucial in directing the reaction towards the desired products. Thus at 30 °C the rate of disappearance of **1** was fast with the formation of two products (detected by ^{1}H-NMR spectroscopy). The desired compound **3** was only produced as a side product. On the basis of the mass spectrum and NMR data, diethyl-piperidine-2,6-dicarboxylate was identified as the main product. In order to avoid hydrogenation of the pyridine ring, the reduction should be carried out at lower temperatures (at 0–5 °C). Under these reaction conditions only the desired compound **3** is formed. In addition, complete reduction of compound **2** can only be achieved if potassium carbonate is added to the reaction mixture. By this means, the hydrobromic acid that is formed in the reaction, and perhaps inhibits further reduction, is neutralized.

To achieve high labelling yields in the deuteration experiments, several provisional measures were taken. All possible sources for potentially introducing hydrogen instead of deuterium atoms into the products had to be excluded. Therefore, all solvents and reactants were carefully dried. The catalyst, palladium black, was heated at 100 °C for 1 d under a vacuum of 0.1 mbar and then stored under an atmosphere of deuterium. Further, a few milliliters of D_2O (99.8%) added to the reaction solution diminish any adverse effects of residual traces of H_2O and also accelerate the reduction of **2** by enhancing the solubility of potassium carbonate. Under such optimized conditions, it is possible to achieve yields of 95 and 98% for the mono- and trideuteration of compound **1** and **2**, respectively. The only side-products detected are **3** or the corresponding dideutero compounds, respectively.

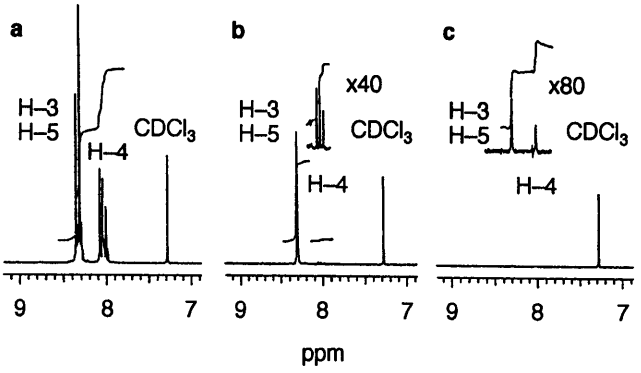


Figure 1: ^{1}H-NMR-signals of the pyridine moiety in the spectra of compounds **3** (a), **4** (b), and **5** (c) in $CDCl_3$.

The extent of deuteration was estimated by ^{1}H NMR spectroscopy. Figure 1 shows the ^{1}H-NMR-spectra for the aromatic protons in compounds **3**, **4** and **5**, obtained by reductive dehalogenation. Thus, the spectrum of the hydrogenation product **3** (Fig. 1a) shows the characteristic A_2B coupling pattern for those signals corresponding to the pyridine hydrogen atoms (3-py-H and 5-py-H: 8.30; 4-py-H: 8.05 ppm). The two protons at the 3- and the 5-positions of the pyridine ring appear in the NMR-spectrum of the monodeuterated compound **4** (Fig. 1b) as one singlet at 8.30 ppm. A considerably less intense signal at 8.05 ppm, associated with the B-portion of the A_2B coupling pattern, indicates the presence of about 4% of compound **3**. On first appearance, no signal can be observed at 8.05 and 8.30 ppm for compound **5** (Fig. 1c). However, an eighty-fold enlargement of the spectrum reveals the presence of two singlets attributed to the 3,4- and 3,5-dideutero compounds. Integration of the signals suggests that the extent of trideuteration is about 98%.

The identities of the deuteration products were further confirmed by the results of ^{13}C-NMR and mass spectroscopy. The ^{13}C-NMR spectra of compounds **4** and **5** provide evidence for successful deuterations because the signal corresponding to the 4-pyridine carbon atom and the two signals corresponding to the 4- and the 3,5-pyridine carbon atoms are each split into triplets due to the D–^{13}C-coupling. The mass peaks of the deuterated molecule ions (M^+) are expected to differ by one and three m/e-units, respectively, from those of the undeuterated compound. Thus, the mass spectra of the compounds **3**, **4** and **5** display very small M^+ peaks at m/e 223, 224, and 226, respectively. Labelling of diethyl-pyridine-2,6-dicarboxylate with one and three deuterium atoms is also evident when the masses of those fragments containing the pyridine moiety arising from compound **3** (m/e 105, 123, 151, 178, 208, 223) are compared with those arising from compounds **4** and **5**.

In summary, a highly effective method for regiospecifically labelling the 4- or 3,4,5-substituents of the pyridine ring in diethyl-pyridine-2,6-carboxylate by deuterium atoms is presented here. The products of the deuterations have been fully characterized.

Materials and Methods

All solvents (p.a. grade), phosphorpentabromide, silica gel 60 (70–230 mesh), and the silica gel glass plates (HPTLC, silica gel 60 F_{254}) were purchased from Merck (Darmstadt). Chelidamic acid (Fluka), D_2O (99.8%, Aldrich), and the catalysts Pd-C (5% and 10%, oxidic form, Merck-Schuchard) and palladium black (Janssen Chimica) were acquired from the indicated sources. Deuterium gas (D_2 99.8%, HD 0.4%) was obtained from Cambridge Isotope Laboratories (Andover, USA). Dichloromethane was freshly distilled from P_2O_5 prior to use. A mixture of dichloromethane/acetone (v:v = 95:5) was used as eluent in thin-layer chromatography. ^1H-NMR and ^{13}C-NMR spectra were recorded on a Varian Gemini 200 NMR-spectrometer. Mass spectra were obtained using a MAT 311 A (70 eV) mass spectrometer.

Preparation of Compounds. Diethyl 4-bromopyridine-2,6-dicarboxylate (**1**) was synthesized from chelidamic acid according to published procedures.[8] Diethyl 3,4,5 tribromopyridine-2,6-dicarboxylate (**2**) was prepared from chelidamic acid by esterification with ethanol in sulfuric acid[11] and by consecutive brominations of the resulting ester with bromine (in a mixture of dichloromethane/ethanol (v:v = 1:1)[12] and then with P_2Br_5.[9]

Synthesis of diethyl pyridine-2,6-dicarboxylate (3): a) by hydrogenation of compound 1. In a 25 mL flask equipped with an inlet for gas, palladium black (250 mg) and potassium carbonate (0.5 g, 3.62 mmol) were suspended in dichloromethane (7 mL) containing compound **1** (500 mg, 1.65 mmol) under an atmosphere of argon. After the argon atmosphere in the flask was changed to a hydrogen atmosphere (0.3–0.4 bar excess pressure), the reaction mixture was stirred vigorously for 1 h at 0 °C. Filtration of the suspension afforded a clear solution, which was flash-chromatographed on a little column containing 250 mg silica gel 60 (70–230 mesh). The product was eluted by a mixture of dichloromethane/acetone (*v*:*v* = 95:5). Evaporation of the solvent and storage of the resulting oil for 1 d at 4°C provided a crystalline product, which was further purified by recrystallization from toluene/petroleum ether. Yield: 350 mg (95%). mp. 45-46 °C (lit. 44-46 °C)[13]. TLC: Rf = 0.4. ^{1}H-NMR ($CDCl_3$): δ = 8.30 (A-portion, J_{AB_2} = 7.8 Hz; 2H; 3-py-H and 5-py-H), 8.05 (B-portion, J_{AB_2} = 7.8 Hz; 1H; 4-py-H), 4.46 (q; 4H; CH_2), 1.45 (t, 6H; CH_3). ^{1}H-decoupled ^{13}C-NMR ($CDCl_3$): δ = 164.6 (s; CO_2), 148.6 (s; C-2 and C-6), 138.2 (s; C-4), 127.8 (s; C-3 and C-5), 62.3 (s; CH_2), 14.2 (s; CH_3). MS (m/e): 223 (0.2%, M^+), 208 (0.2%), 179 (6%), 178 (8%), 177 (0.1%), 152 (8%), 151 (100%), 150 (19%), 123 (18%), 122 (3%),105 (56%), 104 (2%).

b) by hydrogenation of compound 2. Starting with compound **2** (523 mg, 1.14 mmol), a procedure analogous to that for the hydrogenation of **1** was used with the following modifications: a larger amount of potassium carbonate (1.5 g, 10.85 mmol) was employed and the reaction time was extended from 1h to 3 h. Yield: 241 mg (95%).

General provisions for the deuteration procedure. In order to ensure high yields of deuterated compounds, the reactants, dichloromethane, potassium carbonate and the catalyst had to be dried carefully. In addition, the palladium catalyst had to be freed of any residual hydrogen. Therefore the catalyst was heated for prolonged periods at 100 °C in vacuum and then stored under a deuterium atmosphere.

Synthesis of diethyl-4-D-pyridine-2,6-dicarboxylate (4). In a 500 mL-sized flask equipped with a gas inlet, palladium black (6 g), charcoal (5 g), potassium carbonate (40 g, 289 mmol), and deuterium oxide (1 mL) were added to a dichloromethane (200 mL) solution of compound **1** (16.9 g, 55.9 mmol). The gas atmosphere in the flask was changed to deuterium (0.3–0.4 bar excess pressure). The reaction mixture was vigorously stirred at 0–5 °C for 2 d.

The uptake of the deuterium was monitored over this time and the excess pressure of deuterium gas was replenished from the gas bottle. When no further deuterium was consumed, the solid in the reaction mixture was removed by filtration. The clear solution was injected onto a short column of silica gel 60 (5 g). The product was eluted from the column by a mixture of dichloromethane/acetone (*v*:*v* = 95:5). After evaporation of the eluent, the oily product was dissolved in a small amount of toluene. Addition of an excess of petroleum ether yielded the product **4** as a colorless crystalline solid. Based on the relative intensities of the NMR signals corresponding to the 3,5-pyridine hydrogen atoms of **4** and the 4-pyridine hydrogen atom of **3**, the product **4** is contaminated, at most, by 4% of **3**. Yield: 12.0 g (96%). mp. 45-46°C. TLC: R_f = 0.4. ^{1}H-NMR ($CDCl_3$): δ = 8.30 (s, 2H; 3-py-H and 5-py-H), 4.48 (q, 4H; CH_2), 1.46 (t, 6H; CH_3). ^{1}H-decoupled ^{13}C-NMR ($CDCl_3$): δ = 164.1 (s; CO_2), 148.2 (s, C-2 and C-6), 137.8 (t; DC-4), 127.5 (s; C-3 and C-5), 61.9 (s; CH_2), 13.9 (s; CH_3). MS (m/e): 224 (0.17%, M^+), 223 (<0.01%), 209 (0.10%), 208 (<0.01%), 180 (5.4%), 179 (9.14%), 178 (0.19%), 153 (9.01%), 152 (100%), 151 (26.34%), 150 (0.76%), 125 (1.54%), 124 (16%), 123 (4.01%), 107 (9.33%), 106 (64.22%), 105 (4.37%).

Synthesis of diethyl-3,4,5-D_3-pyridine-2,6-dicarboxylate (5). Under an atmosphere of deuterium (0.3–0.4 bar excess pressure), diethyl-3,4,5- tribromopyridine-2,6-dicarboxylate (**2**) (95 g, 207 mmol) in dichloromethane (600 mL) was stirred in a 1L-sized flask in the presence of potassium carbonate (300 g, 2.17 mol), palladium black (6 g), charcoal (5 g), and D_2O (6 mL). The deuterium uptake was monitored over time and compensated for by replenishment from the lecture bottle. After 14 d the reaction was completed. The filtered solution was flash-chromatographed on a silica gel 60 column (20 g) as described previously. The product was obtained by recrystallization from toluene/petroleum ether. Yield 44 g (94%). Based on the relative intensities of the NMR signals corresponding to the hydrogen atoms of the ethyl group and the residual NMR signals corresponding to pyridine protons of only partially deuterated compound (δ = 8.30 (s; 3-py-H), 8.05 (s; 4-py-H) ppm), the extent of deuterium incorporation in the pyridine positions 3, 4 and 5 is calculated to be higher than 98%. mp. 45-46°C. TLC: R_f = 0.4. ^{1}H-NMR ($CDCl_3$): δ = 4.50 (q, 4H; CH_2), 1.46 (t, 6H; CH_3). ^{1}H-decoupled ^{13}C-NMR ($CDCl_3$): δ = 163.9 (s; CO_2), 148.0 (s; C-2, C-6), 137.1 (t; DC-4), 126.8 (t; DC-3 and DC-5), 61.6 (s; CH_2), 13.6 (s; CH_3). MS (m/e): 226 (0.30%, M^+), 225 (0.04%), 211 (0.20%), 182 (5.32%). 181 (9.62%), 180 (0.20%), 154 (100%), 153

(24.9%), 152 (0.61%), 151 (0.04%), 126 (14.5%), 125 (3.32%), 124 (0.07%), 123 (0.08%), 108 (59.54%), 107 (2.32%), 106 (0.80%).

Regeneration of the catalyst. The solid residue obtained from the filtration of the reaction mixture is treated with copious amounts of water to remove the potassium salts. The catalyst recovered by this procedure is first washed with ethanol, dichloromethane and hexane and then dried.

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