Synthesis and Spectroscopic Properties of Some Dideuterated Cyanopyridines

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4-Cyanopyridine-2,6-d_2 (**5a-2,6-d_2**), 3-cyanopyridine-2,6-d_2 (**5b-2,6-d_2**), and 2-cyanopyridine-4,6-d_2 (**5c-4,6-d_2**) were synthesized from the corresponding 2-, 3- or 4-pyridinecarboxylic acid *N*-oxides. These dideuterated products were characterized by their mass and NMR spectra.

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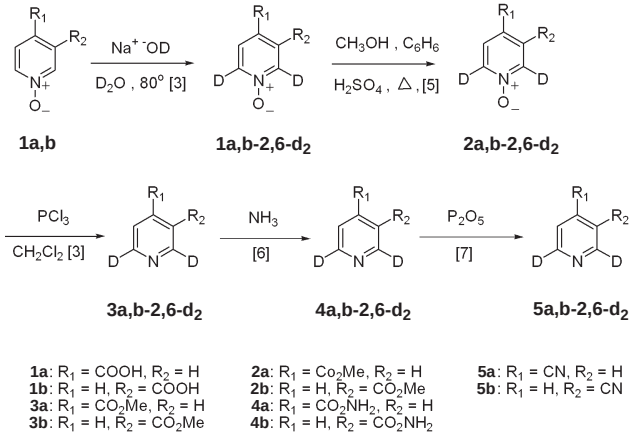
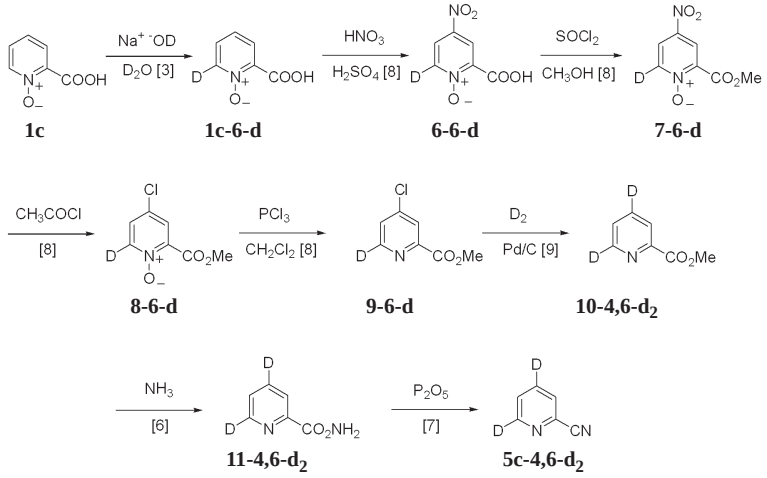
As part of our study of the photochemistry of pyridine and simple substituted pyridines [1,2], samples of the three isomeric cyanopyridines each bearing two deuterium atoms were required. In the case of 3- and 4-substututed pyridines, both open positions α to the nitrogen were readily deuterated by two successive base catalyzed H/D exchanges [3] in the commercially available isonicotinic acid *N*-oxide (**1a**) and nicotinic acid *N*-oxide (**1b**) respectively [4]. In each case, deuteration was confirmed by ^{1}H and ^{13}C-NMR spectroscopy. Thus, the ^{1}H-NMR spectrum of **1a-2,6-d_2** exhibited a singlet at δ 7.79 for the equivalent H3 and H5 protons and only a very small signal at δ 8.87 due to residual hydrogen at ring positions 2 and 6. Furthermore, the singlet in the proton decoupled ^{13}C-NMR spectrum observed at δ 139.0 for the equivalent carbons at ring positions 2 and 6 of **1a** was replaced by a triplet (J ^{13}C-^{2}H = 29.0 Hz) in the spectrum of **1a-2,6-d_2**. NMR spectroscopy also confirmed deuteration at ring positions 2 and 6 of nicotinic acid *N*-oxide (**1b)**. Thus, after deuteration, the ^{1}H-NMR spectrum of **1b-2,6-d_2** exhibited doublets at δ 7.91 and 7.44 (J ^{1}H-^{1}H = 8.0 Hz) for H4 and H5 respectively with very small signals for residual hydrogens at ring positions 2 and 6 while in the ^{13}C-NMR spectrum the singlets at δ 144.0 and 141.9 for C2 and C6 respectively of **1b** were replaced by triplets (J ^{13}C-^{2}H = 28.4 and 26.1 Hz) in the spectrum of **1b-2,6-d_2**.

Scheme 1



Dideuterated isonicotinic acid *N*-oxide (**1a-2,6-d_2**) and nicotinic acid *N*-oxide (**1b-2,6-d_2**) were converted to the corresponding dideuterated 4-cyanopyridine (**5a-2,6-d_2)** and 3-cyanopyridine (**5b-2,6-d_2**) by the functional group conversion reactions shown in Scheme 1.

Scheme 2



In the case of the 2-substituted isomer, which has only one open position α to the nitrogen, a different synthetic approach outlined in Scheme 2 was followed. Thus, commercially available picolinic acid *N*-oxide (**1c)** was subjected to two successive base catalyzed H/D exchanges. Deuteration at ring position 6 was confirmed by NMR spectroscopy. Thus, whereas the ^{1}H-NMR spectrum exhibited a 1H multiplet at δ 7.53 for H4 and a 2H multiplet at δ 7.34 for H3 and H4, only a small signal was observed at δ 8.10 for residual hydrogen at ring position 6. In addition, in the ^{13}C-NMR spectrum the signal due to the C6 carbon was observed as a triplet (J = 28.6 Hz) due to coupling with deuterium. Introduction of deuterium into ring position 4 was accomplished by nitration, replacement of nitro with chloro, and finally deuteriumolysis using D_2 and Pd/C [9,10]. Finally, the ester group was converted to cyano as shown in Scheme 2.

Table 1

^{1}H-NMR Chemical Shifts (δ ppm) of Dideuterated Cyanopyridines

Compound	Ring Position				
	2	3	4	5	6
2-CN-4,6-d_2 ($CDCl_3$)	-	7.66, s	-	7.50, s	-
3-CN-2,6-d_2 ($CDCl_3$)	-	-	7.91, d (J =7.9 Hz)	7.39, d (J =7.9 Hz)	-
4-CN-2,6-d_2 ($CDCl_3$)	-	7.47, s	-	7.47, s	-

According to this fragmentation pattern, 4-cyanopyridine-2,6-d_2 (**5a-2,6-d_2**) should eliminate DCN to leave an m/z =78 fragment. Although this is the major fragment species observed (38% of base peak), the mass spectrum also exhibits a significant peak at m/z =79 (30% of base peak), indicating that the parent species also eliminates HCN. Similar fragmentation patterns were observed in the mass spectra of 3-cyanopyridine-2,6-d_2 (**5b-2,6-d_2**) and 2-cyanopyridine-4,6-d_2 (**5c-4,6-d_2**). This is consistent with the suggestion that a process leading to H/D scrambling precedes fragmentation in the mass spectra of cyanopyridines [11].

The location of the deuterium atoms in the final cyanopyridines was confirmed by the disappearance of signals in the ^{1}H-NMR spectra for the exchanged hydrogen atoms and by the predicted changes in the multiplicities of the remaining protons as summarized in Table 1. As shown in Table 2, the ^{13}C-NMR spectra were particularly useful in confirming the positions of the deuterium atoms since the signals for the carbon atoms bonded to deuterium appear as triplets due to ^{13}C-^{2}H coupling.

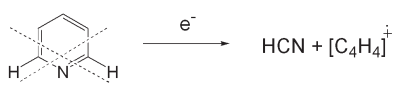
Table 2

^{13}C-NMR Chemical Shifts (δ ppm) of Dideuterated Cyanopyridines

Compound	Ring Position					
	2	3	4	5	6	CN
2-CN-4,6-d_2 ($CDCl_3$)	135.0	129.9	138.2, t (J =25.6 Hz)	128.1	152.2, t (J =28.0 Hz)	118.5
3-CN-2,6-d_2 ($CDCl_3$)	152.5, t (J =27.7 Hz)	110.4	139.7	124.0	153.0, t (J =27.3 Hz)	116.9
4-CN-2,6-d_2 ($CDCl_3$)	151.5, t (J =28.1 Hz)	125.6	120.8	125.6	151.5, t (J =28.1Hz)	116.8

The mass spectrum of the final cyanopyridine products exhibited molecular ions at m/z = 106 confirming the incorporation of two deuterium atoms into each compound. According to mass spectral studies of pyridine and simple substituted pyridines, the major fragmentation pathway involves elimination of H–C_α≡N leaving an M^+-27 fragment species. Indeed, the major fragmentation signal in the mass spectrum of pyridine is observed at m/z = 52 (79 % of base peak).

Scheme 3



EXPERIMENTAL

^{1}H and ^{13}C spectra were recorded at 400.1 and 100.6 MHz in deuteriochloroform on a Bruker FT-NMR system. ^{1}H and ^{13}C chemical shifts were measured relative to internal tetramethylsilane and chloroform, respectively. Mass spectra were recorded with an HP 5970B mass selective detector interfaced to an HP 588 capillary gas chromatograph.

Isonicotinic Acid *N*-oxide-2,6-d_2 (**1a-2,6-d_2**), Nicotinic Acid *N*-oxide-2,6-d_2 (**1b-2,6-d_2**), and Picolinic Acid N-oxide-6-d (**1c-6d**).

The open positions α to nitrogen were deuterated by treatment of **1a**, **1b**, or **1c** (3.0 g, 21.6 mmol) in deuterium oxide (10.0 mL) containing sodium deuteroxide from sodium metal (0.71 g, 31.0 mmol). After 4 hr. at 80 °C the cooled solution was acidified (conc. hydrochloric acid). The resulting precipitate of partially deuterated **1a**, **1b**, or **1c** was subjected to a second hydrogen-deuterium exchange as above. Acidification as above gave **1a-2,6-d_2**, **1b-2,6-d_2**, or **1c-6-d** as white solids.

Compound **1a-2,6-d_2** was obtained in a yield of 2.9 g (20.6 mmol, 95.5 %); ^{1}H-NMR (deuterium oxide) δ 7.69 (s, 2H); ^{13}C-

NMR (deuterium oxide) δ (DEPT–135) 170.6 (0), 139.6 (0), 139.0 (t, *J* = 29.0 Hz)(0), 127.0 (+).

Compound **1b-2,6-d_2** was obtained in a yield of 2.9 g (20.6 mmol, 95.5 %); ^{1}H-NMR (deuterium oxide) δ 7.91 (d, 1H, *J* = 8.0 Hz), 7.44 (d, 1H, J = 8.0 Hz); ^{13}C-NMR (deuterium oxide) δ (DEPT-135) 168.2 (0), 144.0 (t, *J* = 28.4 Hz)(0), 141.9 (t, *J* = 26.1 Hz)(0), 135.1(0), 133.8(0), 129.3(+).

Compound **1c-2,6-d_1** was obtained in a yield of 1.96 g from 2.0 g (14.0 mmol, 95.2 %); ^{1}H-NMR (deuterium oxide) δ 7.53 (m, 1H), 7.34 (m, 2H); ^{13}C-NMR (deuterium oxide) δ (DEPT-135) 168.0(0), 147.7(0), 139.0(t, *J* = 28.6 Hz)(0), 132.6 (+), 126.2 (+), 124.0 (+).

Methyl Isonicotinate *N*-oxide-2,6-d_2 (**2a-2,6-d_2**) and Methyl Nicotinate N-oxide-2,6-d_2 (**2b-2,6-d_2**).

Compounds **1a-2,6-d_2** or **1b-2,6-d_2** (2.9 g, 20.6 mmol) were refluxed in a mixture of benzene (10 mL), methanol (10 mL), and conc. sulfuric acid (2 mL) followed by azeotropic distillation. The residue was poured onto ice (10 g), made basic with aqueous sodium carbonate (10 %), extracted with dichloromethane (5 x 20 mL) and the dried extract (sodium sulfate) evaporated to provide the esters.

Compound **2a-2,6-d_2** was obtained in a yield of 1.3 g (8.4 mmol, 41 %); ^{1}H-NMR (deuteriochloroform) δ 7.79 (s, 2H), 3.88 (s, 3H); ^{13}C-NMR (deuteriochloroform) δ (DEPT-135) 164.2(0), 139.6(t, *J* = 29.0 Hz)(0), 126.8(0), 126.7 (+), 53.2 (+).

Compound **2b-2,6-d_2** was obtained in a yield of 1.8 g (11.8 mmol, 56%); ^{1}H-NMR (deuteriochloroform) δ 7.81 (d, 1H, *J* = 8.0 Hz), 7.41 (d, 1H, *J* = 8.0 Hz); ^{13}C-NMR (deuteriochloroform) δ (DEPT-135) 163.5(0), 142.5 (t, *J* = 28.4 Hz)(0), 140.1 (t, *J* = 29.1 Hz)(0), 132.2 (0), 126.9 (+), 126.2 (+), 53.8 (+).

Methyl Isonicotinate-2,6-d_2 (**3a-2,6-d_2**) and Methyl Nicotinate-2,6-d_2 (**3b-2,6-d_2**).

Methyl isonicotinate *N*-oxide-2,6-d_2 (**2a-2,6-d_2**) (1.4 g, 9.0 mmol) or methyl nicotinate *N*-oxide-2,6-d_2 (**2b-2,6-d_2**) (1.2 g, 7.7 mmol) dissolved in dichloromethane (60 mL) was added dropwise to phosphorus trichloride (1.2 mL) at 0 °C. The mixture was refluxed for 1 hr, mixed with ice water (30 mL), made alkaline with aqueous NaOH (10 *N*) and extracted with dichloromethane (5 x 20 mL). Evaporation of the dried (sodium sulfate) solution gave methyl isonicotinate-2,6-d_2 (**3a-2,6-d_2**) or methyl nicotinate-2,6-d_2 (**3b-2,6-d_2**).

Compound **3a-2,6-d_2** was obtained in a yield of 0.9 g (6.5 mmol, 72 %); ^{1}H-NMR (deuteriochloroform) δ 7.73 (s, 2H), 3.86 (s, 3H); ^{13}C-NMR (deuteriochloroform) δ (DEPT-135) 165.7 (0), 150.3 (t, *J* =27.6 Hz)(0), 137.7(0), 123.1(t), 53.0 (+); MS m/z (%) 139 (100), 108 (90).

Compound **3b-2,6-d_2** was obtained in a yield of 0.92 g (6.6 mmol, 85 %); ^{1}H-NMR (deuteriochloroform) δ 8.98 (d, 1H, J = 8.1 Hz), 8.17 (d, 1H, J = 8.1 Hz), 4.01 (s, 3H); ^{13}C-NMR (deuteriochloroform) δ (DEPT-135) 162.1(0), 146.3(+), 144.6(t, J = 29.1 Hz)(0), 142.3(t, J = 29.5 Hz)(0), 130.2(0), 127.8(+), 54.2(+); MS m/z (%) 139 (100), 108 (90).

Isonicotinamide-2,6-d_2 (**4a-2,6-d_2**).

Methyl isonicotinate-2,6-d_2 (**3a-2,6-d_2**) (0.97 g, 6.5 mmol) dissolved in methanol (3 mL) was added dropwise to conc. aqueous ammonia (10 mL). The resulting cloudy solution was made clear by addition of methanol (~ 80 mL). After 5 h at room temp the solution was cooled in the freezer overnight. Evaporation gave isonicotinamide-2,6-d_2 (**4a-2,6-d_2**) as a white solid.

Compound **4a-2,6-d_2** was obtained in a yield of 0.64 g (5.2 mmol, 80 %); ^{1}H-NMR (deuterium oxide) δ 7.53 (s, 2H); ^{13}C-NMR (deuterium oxide) δ (DEPT-135) 170.6 (0), 148.9 (t, *J* = 27.9 Hz)(0), 142.1(0), 122.1(+).

Nicotinamide-2,6-d_2 (**4b-2,6-d_2**).

Methyl nicotinate-2,6-d_2 (**3b-2,6-d_2**)(0.76 g, 5.4 mmol) was dissolved in cold, conc. aqueous ammonia (2 mL) at 0 °C. The flask was capped and allowed to stand at room temperature for 5 h during which additional ammonia (1 mL) was added every hour. The solution was then stored in the refrigerator for 4 days. Evaporation gave nicotinamide-2,6-d_2 (**4b-2,6-d_2**) as a light brown solid.

Compound **4b-2,6-d_2** was obtained in a yield of 0.42 g (3.4 mmol, 63 %); ^{1}H-NMR (deuterium oxide) δ 7.97 (d, 1H, J = 8.0 Hz), 7.32 (d, 1H, J = 8.0 Hz); ^{13}C-NMR (deuterium oxide) δ (DEPT-135) 170.9(0); 151.9(t, *J* = 27 Hz)(0), 147.5 (t, *J* = 27.0 Hz)(0), 136.7(+), 129.4(0), 124.3(+).

4-Cyanopyridine-2,6-d_2 (**5a-2,6-d_2**) or 3-Cyanopyridine-2,6-d_2 (**5b-2,6-d_2**).

Isonicotinamide-2,6-d_2 (**4a-2,6-d_2**) (0.23 g, 1.9 mmol) or nicotinamide-2,6-d_2 (**4b-2,6-d_2**) (0.42 g, 3.4 mmol) and phosphorous pentoxide (0.52 g, 3.8 mmol or 1.0 g, 7.0 mmol, respectively) was heated in a round bottom flask in a Kugelrohr oven at 160-180 °C for 3 h. In the case of **4a-2,6-d_2** the cooled mixture was extracted with dichloromethane (5 x 20 mL). The dried extract (sodium sulfate) was evaporated. The solid residue (0.15 g) was sublimed (70 °C, water aspirator) to give 4-cyanopyridine-2,6-d_2 (**5a-2,6-d_2**). In the case of **4b-2,6-d_2**, the reaction with phosphorous pentoxide at 160-180 °C was continued for 3 h during which the product was allowed to sublime out of the reaction mixture at reduced pressure (water aspirator) and trapped in a bulb submerged in dry ice to give 3-cyanopyridine-2,6-d_2 (**5b-2,6-d_2**).

Compound **5a-2,6-d_2** was obtained in a yield of 0.07 g (0.6 mmol, 32 %). For NMR data see Tables 1 and 2.

Compound **5b-2,6-d_2** was obtained in a yield of 0.10 g (0.9 mmol, 27 %). For NMR data see Tables 1 and 2.

4-Nitropicolinic Acid *N*-oxide-6-d (**6-6-d**).

Picolinic acid *N*-oxide-6-d (**1c-6-d**) (1.92 g, 13.7 mmol) was dissolved in a mixture of fuming nitric acid (3.3 mL) and conc. sulfuric acid (12 mL) and heated in an oil bath until the solution refluxed and the temperature remained between 120-127 °C for 1 h. The resulting mixture was diluted with water (70 mL) and after gas evolution ceased it was stored in a freezer overnight. Filtration gave 4-nitropicolinic acid *N*-oxide-6-d (**6-6-d**) as light yellow crystals, m.p. 148 °C.

Compound **6-6-d** was obtained in a yield of 1.14 g (6.2 mmol, 45.2 %); ^{1}H-NMR (dimethylsulfoxide-d_6) δ 8.52 (s, 1H), 8.35 (s, 1H); ^{13}C-NMR (dimethylsulfoxide-d_6) δ (DEPT-135) 165.0 (0), 154.5 (0), 152.4 (t, *J* = 28.4 Hz), 151.3 (0), 119.7 (+), 117.4 (+).

Methyl 4-Nitropicolinate *N*-oxide-6-d (**7-6-d**).

4-Nitropicolinic acid *N*-oxide-6-d (**6-6-d**) (0.91 g, 1.0 mmol) and thionyl chloride (0.18 mL) was heated to reflux with stirring. Methanol (5 mL) was added and the resulting solution was heated to reflux for 1 h. Cooling the solution gave methyl 4-nitropicolinate *N*-oxide-6-d (**7-6-d**) as yellow crystals, m.p. 136 °C.

Compound **7-6-d** was obtained in a yield of 0.11 g (0.6 mmol, 60 %) ; ^{1}H-NMR (deuteriochloroform) δ 8.56 (s, 1H), 8.17 (s, 1H), 4.03 (s, 3H); ^{13}C-NMR (deuteriochloroform) δ (DEPT-135) 160.3 (0), 142.4 (t, *J* = 28.8 Hz)(0), 142.1(0), 122.8(+), 122.0(+), 54.2(+).

Methyl 4-Chloropicolinate *N*-oxide-6-d (**8-6-d**).

Acetyl chloride (4.1 mL) was added dropwise to methyl 4-nitropicolinate *N*-oxide-6-d (**7-6-d**) (0.81 g, 4.1 mmol) at 40 °C. After gas evolution ceased the solution was cooled to rt and concentrated to dryness (0.85 g). Flash column chromatography (silica gel) using dichloromethane gave methyl 4-chloropicolinate N-oxide-6-d (**8-6-d**) as white crystals, m.p. 112 °C.

Compound **8-6-d** was obtained in a yield of 0.65 g (3.4 mmol, 83 %); ^{1}H-NMR (deuteriochloroform) δ 7.56 (s, 1H), 7.33 (s, 1H), 3.99 (s, 3H); ^{13}C-NMR (deuteriochloroform) δ (DEPT-135) 161.2 (0), 142.3 (0), 141.8 (t, *J* = 29.1 Hz)(0), 131.4 (0), 128.1 (+), 127.5 (+), 54.0 (+).

Methyl 4-Chloropicolinate-6-d (**9-6-d**).

Methyl 4-chloropicolinate *N*-oxide-6-d (8-6-d)(0.42 g, 2.2 mmol) in dichloromethane (20 mL) was added dropwise to phosphorous trichloride (1 mL) at 0 °C with stirring. The resulting solution was heated at reflux for 1 h, poured onto ice (20 g), made basic with aqueous sodium hydroxide (10 *N*), extracted with dichloromethane (5 x 20 mL), and dried (sodium sulfate). Evaporation gave methyl 4-chloropicolinate-6-d (**9-6-d**) as a yellow liquid.

Compound **9-6-d** was obtained in a yield of 0.34 g (1.9 mmol, 87 %); ^{1}H-NMR (deuteriochloroform) δ 8.20 (s, 1H), 7.67 (s, 1H), 3.99 (s, 3H); ^{13}C-NMR (deuteriochloroform) δ (DEPT-135) 163.6 (0), 149.4 (t, *J* = 28.2 Hz)(0), 148.2(0), 128.3(+), 126.7(+), 54.0(+).

Methyl Picolinate-4,6-d_2 (**10-4,6-d_2**).

Methyl 4-chloropicolinate-6-d (**9-6-d**) (0.20 g, 1.2 mmol) dissolved in methanol-OD (15 mL) was placed in a Büchner flask containing potassium carbonate (0.16 g), Pd-C (10 %, 0.030 g), and a magnetic stirring bar. The flask was sealed with a septum and equipped with a balloon at the side arm. A side-arm test tube containing sodium (0.5 g) was sealed with a septum and the side-arm was connected to the Büchner flask. The entire system was purged with nitrogen for 10 min. Deuterium oxide (2.0 mL) was then added through the septum to the sodium in the side-arm test tube. The deuterium gas generated filled the system and caused the balloon to expand. The reaction mixture in the Büchner flask was stirred in the deuterium atmosphere for 4 h. The Pd-C was removed by filtration and the filtrate was evaporated and the residue dissolved in dichloromethane (70 mL) which was washed with water (2 x 10 mL), dried (sodium sulfate) and evaporated to give methyl picolinate-4,6-d_2 (**10-4,6-d_2**) as a colorless liquid.

Compound **10-4,6-d_2** was obtained in a yield of 0.14 g (1.0 mmol, 83 %); ^{1}H-NMR (deuteriochloroform) δ 8.16 (s, 1H), 7.50 (s, 3H); 4.02 (s, 3H); ^{13}C-NMR (deuteriochloroform) δ (DEPT-135) 165.7(0), 149.5(t, *J* = 27.6 Hz)(0), 147.9(0), 136.8(t, *J* = 25.1 Hz)(0), 126.8(+), 125.1(+), 52.9(+); MS m/z (%) 139(4.5), 81(92).

Picolinamide-4,6-d_2 (**11-4,6-d_2**).

Methyl picolinate-4,6-d_2 (**10-4,6-d_2**)(1.04 g, 7.5 mmol) was dissolved in cold, conc. aqueous ammonia (20 mL). A second portion of aqueous ammonia (10 mL) was added and the mixture was stored in the freezer overnight. Evaporation gave picolinamide-4,6-d_2 (**11-4,6-d_2**) as a white solid, m.p. 122 °C.

Compound **11-4,6-d_2** was obtained in a yield of 0.61 g (4.9 mmol, 65 %); ^{1}H-NMR (deuteriochloroform) δ 8.22 (s, 1H), 7.90 (broad, 1H), 7.46 (s, 1H), 6.18 (broad, 1H); ^{13}C-NMR (deuteriochloroform) δ (DEPT-135) 167.4 (0), 149.9(0), 148.4(t, *J* = 25.2 Hz), 137.7(t, *J* = 20.1 Hz), 126.6(+), 122.7(+).

2-Cyanopyridine-4,6-d_2 (**5c-4,6-d_2**).

A mixture of picolinamide-4,6-d_2 (**11-4,6-d_2**)(0.20 g, 1.6 mmol) and phosphorous pentoxide (0.7 g, 4.9 mmol) was heated slowly in a Kugelrohr oven from 120-190 °C at a pressure of 0.1 Torr. The 2-cyanopyridine-4,6-d_2 (**5c-4,6-d_2**) was collected in the receiving flask. Purification by flash column chromatography using dichloromethane/ ethyl acetate (1:1) gave 2-cyanopyridine-4,6-d_2 (**5c-4,6-d_2**) as a colorless liquid.

Compound **5c-4,6-d_2** was obtained in a yield of 0.07 g (0.70 mmol, 41 %). For NMR data see Tables 1 and 2.

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