# Strategies for the Selective Functionalization of Dichloropyridines at Various Sites

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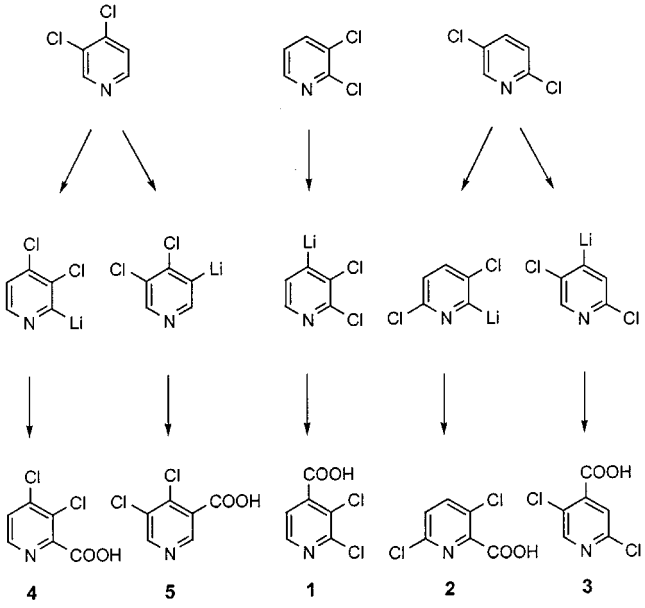
Whereas 2,3-dichloropyridine and 2,5-dichloro-4-(lithiooxy)-pyridine undergo deprotonation exclusively at the 4- and 2-positions, respectively, optional site selectivity can be implemented with 2,5- and 3,4-dichloropyridine (which are attacked, depending on the choice of the reagents, at either the 4- or 6- and either the 2- and 5-positions, respectively). Upon treatment with lithium diisopropylamide, 2,4-dichloro-3-iodopyridine, 3,5-dichloro-4-bromopyridine and 2,6-dichloro-3-iodopyridine afford 5-, 2- and 4-lithiated intermediates, but the latter isomerize instantaneously to species in which lithium and iodine have swapped places, the driving force being the low basicity of C–Li bonds when flanked by two neighboring halogens.

## Introduction

A solution of lithium diisopropylamide (LIDA) in tetrahydrofuran (THF) promotes a clean hydrogen/metal exchange (metalation) at the 3- or 4-positions adjacent to the halogen of 2-, 3- and 4-chloropyridine.[1–3] 2,4-[4] and 3,5-Dichloropyridines[5] undergo lithiation exclusively at the position flanked by the two halogen atoms, thus affording 3- and 4-substituted derivatives, respectively, although the latter are only formed in poor yields (29%). On the other hand, 2,6-dichloropyridine tends to form mixtures of 3- and 4-isomers, for example in the ratios of 2:1 and 1:5 after treatment with lithium diisopropylamide (LIDA) or *sec*-butyllithium, respectively, for 30 min. in tetrahydrofuran at −80 °C followed by trapping with benzaldehyde.[4] However, prolongation of the interaction with LIDA,[4] or the use of phenyllithium,[3] appear to give rise to relatively pure 3-isomers.

When entering this area, we fixed ourselves three objectives: we expected to extend the metalation studies to the three remaining dichloropyridines, hopefully to identify new examples of "optional site selectivity"[6] and to explore other possibilities for the conversion of a given precursor compound into two (or more) different organolithium species.

Attempts to establish optional site selectivities by simply varying the reagents and reaction conditions are doomed to failure whenever the deprotonation of one position is so favored that none of the others has a chance to compete. No matter whether lithium diisopropylamide or butyllithium was used as the base, 2,3-dichloropyridine underwent deprotonation exclusively at the 4-position (Scheme 1). Subsequent trapping with dry ice afforded the acid **1** in almost quantitative yield (96%). The regioisomeric acids **2** (58%) and **3** (87%) were obtained without mutual contamination when 2,5-dichloropyridine was treated with *tert*-butyllithium or with *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA)-activated butyllithium, respectively. 3,4-Dichloropyridine reacted with lithium 2,2,6,6-tetramethylpiperidide (LITMP) in diethyl ether at −75 °C mainly at the 2-position and with LIDA, in THF at −75 °C, exclusively at the 5-position providing, after carboxylation, the acids **4** and **5** (both isolated as their methyl esters in 42% and 64% yields, respectively).




Scheme 1

The electrophile, of course, does not affect the regioselectivity established in the irreversible metalation step. Thus, 2,5-dichloro-4-pyridyllithium reacted with *N*,*N*-dimethylformamide (Scheme 2) to give 2,5-dichloro-2-pyridinecarboxaldehyde (**6**; 80%), while a borylation/oxidation sequence[7] provided the pyridone (**7**; 69%). Metalation of the

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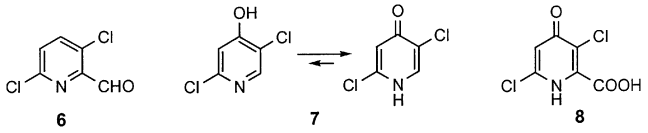
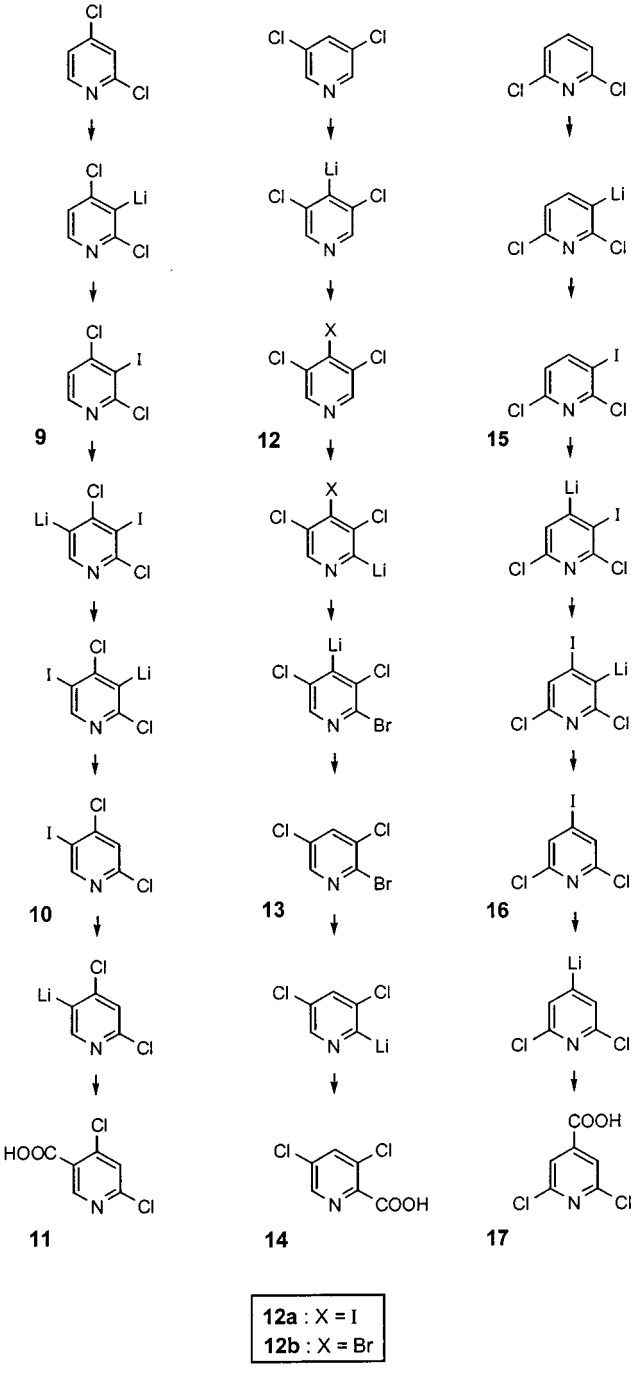
latter with two equivalents of *tert*-butyllithium and carboxylation afforded the acid **8** (58%).



Scheme 2

Let us consider again the three dichloropyridines which had been previously investigated by other researchers (see above). Chlorine atoms acidify C−H bonds in their immediate vicinity more strongly than at greater distance and the effects of two halogens are cumulative. As already pointed out, the clean deprotonation of 2,4-dichloropyridine can hence only be achieved at the 3-position, that of 2,6-dichloropyridine again at the 3-position and of 3,5-dichloropyridine at the 4-position. Other positions are nevertheless amenable to lithiation if one chooses an indirect approach. The key step can be in numerous cases the metal-driven, basicity-lowering halogen migration which has previously been successfully applied to the specific isomerization of aromatic[8] and five-membered[9−13] or six-membered[14−15] heterocyclic organolithium intermediates. When 2,4-dichloro-3-pyridyllithium, generated from 2,4-dichloropyridine with LIDA,[4] was intercepted with elemental iodine, 2,4-dichloro-3-iodopyridine formed in high yield (Scheme 3; **9**, 81%). When, in turn, this compound was treated with LIDA, metalation took place at the sole halogen-adjacent unoccupied position. However, the resulting 2,4-dichloro-3-iodo-5-pyridyllithium instantaneously isomerized to the less basic 2,4-dichloro-5-iodo-3-pyridyllithium, trace amounts of 2,4-dichloro-3,5-diiodopyridine presumably acting as the catalytic turntable.[16] After neutralization, 2,4-dichloro-5-iodopyridine (**10**) was isolated (26%). When the latter compound was submitted to a halogen/metal exchange with butyllithium or *tert*-butyllithium, 2,4-dichloro-5-pyridyllithium was produced which was trapped as the 2,4-dichloro-5-pyridinecarboxylic acid (Scheme 3; **11**; 79%). The attempted base-promoted isomerization of 3,5-dichloro-4-iodopyridine (**12a**:X = I, 64%) failed due to the total insolubility of this compound in ethereal solvents. Therefore, 3,5-dichloropyridine was converted into 4-bromo-3,5-dichloropyridine (Scheme 3; **12b**: X = Br, 86%) and the latter isomerized to 2-bromo-3,5-dichloropyridine (**13**, 42%). Consecutive treatment with *tert*-butyllithium (2.0 equiv.) and dry ice gave 3,5-dichloro-2-pyridinecarboxylic acid (**14**; 88%). Similarly, 2,6-dichloro-4-pyridinecarboxylic acid (Scheme 3; **17**; 89%) was synthesized by consecutive treatment of 2,6-dichloro-4-iodopyridine (**16**; 68%; prepared from 2,6-dichloropyridine, **15**, 72%) with butyllithium and dry ice.

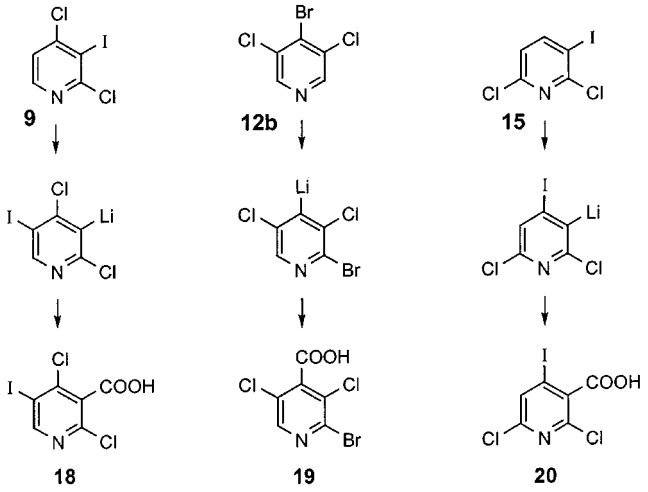
Rather than quenching the intermediates formed upon iodine/lithium countercurrent migration with water, one can of course trap them with a variety of other electrophiles. As an illustration of this possibility, 2,4-dichloro-5-iodo-3-pyridyllithium, 2-bromo-3,5-dichloro-4-pyridyllithium and 2,6-dichloro-4-iodo-3-pyridyllithium were converted into




Scheme 3

the carboxylic acids **18**−**20** (Scheme 4; 25%, 41% and 57%, respectively).

As the present study demonstrates, a few simple chloro- and dichloropyridines can be efficiently and regioselectively converted into a number of di- and trihalogenated pyridinecarboxylic acids, most of them unknown so far. To achieve such structural diversity, we relied on the combination of two tactics: "optional site selectivity"[6] and "basicity gradient-driven halogen migration". Several impressive examples of the latter reaction mode have previously been reported by Quéguiner et al. in the pyridine[14] and quinoline[15] series. We are presently exploring a further method of intro-




Scheme 4

ducing a metal at a given position. Bromine can be used to temporarily replace and thus "protect" a hydrogen atom, which, otherwise, would be abstracted as a proton and, at the same time, to activate centers in its vicinity towards base attack. We shall address this issue in forthcoming publications.[17]

## Experimental Section

**General Remarks:** Details concerning standard operations and the meaning of abbreviations can be found in previous publications from this laboratory.[18,19] $^1$H and $^{13}$C NMR spectra were recorded at 400 and 101 MHz, respectively. The solvent was $CDCl_3$ or, occasionally (marked with an asterisk), [$D_6$]DMSO.

**Starting Materials. – Dichloropyridines:** 2,3-, 2,5-, 2,6- and 3,5-Dichloropyridine are commercially available. The two missing isomers were prepared applying new methods.

**3,4-Dichloropyridine:** At −75 °C, diisopropylamine (14 mL, 10 g, 0.10 mol) and 3-chloropyridine (9.4 mL, 11 g, 0.10 mol) were consecutively added to butyllithium (0.10 mol) in tetrahydrofuran (140 mL) and hexanes (60 mL). After 2 h at −75 °C, the mixture was treated for 1 h at −75 °C with 1,1,2-trichloro-1,2,2-trifluoroethane (12 mL, 19 g, 0.10 mol). Distillation afforded a viscous liquid which crystallized in the freezer as white needles; 11.2 g (76%); m.p. 22−23 °C (ref.[20] 22−23 °C). – $^1$H NMR: δ = 8.55 (s, 1 H), 8.41 (d, $J$ = 5.4 Hz, 1 H), 7.43 (d, $J$ = 5.4 Hz, 1 H). – $^{13}$C NMR: δ = 150.2, 148.1, 141.9, 130.7, 125.1.

**2,4-Dichloropyridine:** 2-Chloro-4-iodopyridine (see below; 24 g, 0.10 mol) was added to an ice-cold solution of isopropylmagnesium chloride (0.10 mol) in tetrahydrofuran. After 1 h at 0 °C, the mixture was brought to +25 °C and treated with spatula tip portions of *N*-chlorosuccinimide (13 g, 0.10 mol) in the course of 60 min. After addition of a saturated aqueous solution of ammonium chloride, a steam distillation was performed. The product (8.9 g, 67%) was isolated as a colorless liquid after extraction with dichloromethane and distillation; bp 78−79 °C/24 Torr (ref.[21] 73−75 °C/15 Torr). – $n_D^{20}$ = 1.5485. – $^1$H NMR: δ = 8.29 (d, $J$ = 5.4 Hz, 1 H), 7.35 (d, $J$ = 1.8 Hz, 1 H), 7.23 (dd, $J$ = 5.4, 1.8 Hz, 1 H). – $^{13}$C NMR: δ = 152.3, 150.2, 145.8, 124.5, 123.0.

**Intermediates: Mono- and Dichlorinated Iodo- (and Bromo-)pyridines**

**2-Chloro-4-iodopyridine:** At −75 °C, diisopropylamine (21 mL, 15 g, 0.15 mol) and 2-chloro-3-iodopyridine (see below; 36 g, 0.15 mol) were consecutively added to butyllithium (0.15 mol) in tetrahydrofuran (200 mL) and hexanes (100 mL). After 4 h at −75 °C, the mixture was poured into water (200 mL) and extracted with diethyl ether (3 × 100 mL). The residue left behind after evaporation of the organic solvent was steam distilled. A white solid (28.4 g, 79%) was collected and dried in a desiccator; m.p. 42−44 °C (ref.[22] 38−39 °C). – $^1$H NMR: δ = 8.07 (d, $J$ = 5.3 Hz, 1 H), 7.76 (d, $J$ = 1.1 Hz, 1 H), 7.59 (dd, $J$ = 5.0, 1.1 Hz, 1 H). – $^{13}$C NMR: δ = 151.7, 149.7, 133.0, 131.5, 106.6.

**2-Chloro-3-iodopyridine:** At −75 °C, 2,2,6,6-tetramethylpiperidine (34 mL, 28 g, 0.20 mol) and 2-chloropyridine (19 mL, 23 g, 0.20 mol) were consecutively added to butyllithium (0.20 mol) in tetrahydrofuran (270 mL) and hexanes (130 mL). After 2 h at −75 °C, the mixture was treated with a solution of iodine (51 g, 0.20 mol) in tetrahydrofuran (100 mL) before being partitioned between water (200 mL) and diethyl ether (3 × 100 mL). The combined organic layers were washed with 1.0 M hydrochloric acid (2 × 75 mL) and a saturated aqueous solution of sodium thiosulfate (2 × 75 mL). The organic solvent was evaporated and the residue submitted to a steam distillation, after which a white solid (36.5 g, 76%) was collected; m.p. 91−93 °C (ref.[23] 90 °C). – $^1$H NMR: δ = 8.38 (dd, $J$ = 4.6, 1.7 Hz, 1 H), 8.16 (dd, $J$ = 7.9, 1.6 Hz, 1 H), 6.96 (dd, $J$ = 7.9, 4.7 Hz, 1 H). – $^{13}$C NMR: δ = 154.5, 148.9, 148.8, 123.2, 94.9.

**2,4-Dichloro-3-iodopyridine (9):** At −75 °C, diisopropylamine (3.5 mL, 2.5 g, 25 mmol) and 2,4-dichloropyridine (3.7 g, 25 mmol) were consecutively added to butyllithium (25 mmol) in tetrahydrofuran (35 mL) and hexanes (16 mL). After 2 h at −75 °C, the mixture was treated with iodine (7.4 g, 25 mmol), dissolved in tetrahydrofuran (25 mL), and worked up as described in the preceding paragraph; m.p. 89−90 °C; 5.6 g (81%). – $^1$H NMR: δ = 8.22 (d, $J$ = 5.2 Hz, 1 H), 7.30 (d, $J$ = 5.2 Hz, 1 H). – $^{13}$C NMR: δ = 156.9, 151.3, 148.6, 122.5, 100.8. – $C_5H_2Cl_2IN$ (273.89): calcd. C 21.93, H 0.74; found C 21.79, H 0.98.

**2,6-Dichloro-3-iodopyridine (15):** Analogously, as described in the preceding paragraph, starting with 2,6-dichloropyridine (3.7 g, 25 mmol). The product was isolated in the form of colorless platelets, without steam distillation, by evaporation of the washed ethereal extract and recrystallization from hexanes; m.p. 76−77 °C; 4.9 g (72%). – $^1$H NMR: δ = 8.06 (d, $J$ = 8.1 Hz, 1 H), 7.01 (d, $J$ = 8.1 Hz, 1 H). – $^{13}$C NMR: δ = 153.9, 150.5, 150.3, 124.0, 92.5. – $C_5H_2Cl_2IN$ (273.89): calcd. C 21.93, H 0.74; found C 22.07, H 0.96.

**3,5-Dichloro-4-iodopyridine (12a, X = I):** Analogously from 3,5-dichloropyridine (3.7 g, 25 mmol); m.p. 183−184 °C (ref.[24] 183 °C); 4.4 g (64%). – $^1$H NMR: δ = 8.38 (s, 2 H). – $^{13}$C NMR: δ = 145.5 (2 C), 137.6 (2 C), 116.1.

**4-Bromo-3,5-dichloropyridine (12b, X = Br):** At −75 °C, diisopropylamine (14 mL, 10 g, 0.10 mol) and 3,5-dichloropyridine (15 g, 0.10 mol) were consecutively added to butyllithium (0.10 mol) in tetrahydrofuran (130 mL) and hexanes (70 mL) After 2 h at −75 °C, the mixture was cooled to −100 °C and treated with bromine (5.1 mL, 16 g, 0.10 mol). After 3 h at −75 °C, it was steam distilled. The product was obtained as white prisms (19.5 g, 86%); m.p. 75−76 °C. – $^1$H NMR: δ = 8.48 (s, 2 H). – $^{13}$C NMR: δ = 147.2 (2 C), 134.0, 133.2 (2 C). – $C_5H_2BrCl_2N$ (226.89): calcd. C 26.47, H 0.89; found C 26.25, H 1.03.

**2,4-Dichloro-5-iodopyridine (10):** At −75 °C, a stirred solution of lithium diisopropylamide (prepared from diisopropylamine and bu-

tyllithium, 25 mmol each) in tetrahydrofuran (15 mL) and hexanes (15 mL) was added dropwise, over 15 min., to 2,4-dichloro-3-iodopyridine (**9**; 6.8 g, 25 mmol) dissolved in tetrahydrofuran (20 mL). After 2 h at −75 °C, water (2.5 mL) was added and the mixture was absorbed on silica gel (25 mL). The powder, when dry, was poured on top of a wet column filled with more silica (125 mL). Elution with a 1:4 (v/v) mixture of dichloromethane and hexanes gave colorless needles (1.8 g, 26%); m.p. 52−54 °C (after sublimation). − $^1$H NMR: δ = 8.71 (s, 1 H), 7.48 (s, 1 H). − $^{13}$C NMR: δ = 157.5, 151.9, 149.8. 125.0, 95.6. − $C_5H_2Cl_2IN$ (273.89): calcd. C 21.93, H 0.74; found C 22.00, H 0.70.

**2,6-Dichloro-4-iodopyridine (16):** Analogously, as described in the preceding paragraph, from 2,6-dichloro-3-iodopyridine (**15**; 6.8 g, 25 mmol). The product was isolated, after addition of water, by extraction with diethyl ether and recrystallization from hexanes in the form of colorless platelets (4.7 g, 68%); m.p. 159−161 °C (ref.[25] 160 °C). − $^1$H NMR: δ = 8.06 (s, 2 H). − $^{13}$C NMR: δ = 149.2 (2 C), 131.6 (2 C), 111.3.

**2-Bromo-3,5-dichloropyridine (13):** At −100 °C and under stirring, a solution of diisopropylamide (prepared from diisopropylamine and butyllithium, 25 mmol each) in tetrahydrofuran (10 mL) and hexanes (15 mL) was added dropwise, in the course of 15 min., to 4-bromo-3,5-dichloropyridine (**12b**; X = Br; 5.7 g, 25 mmol) dissolved in tetrahydrofuran (25 mL). After 1 h at −75 °C, the reaction mixture was absorbed on silica gel (25 mL) and the powder, once dried, poured on top of a column filled with wet silica gel (125 mL). A 3:7 (v/v) mixture of dichloromethane and hexanes eluted first 2,6-dibromo-3,5-dichloropyridine [7%; m.p. 96−97 °C; ref. m.p.[26] 93−95 °C. − $^1$H NMR: δ = 7.80 (s, 1 H). − $^{13}$C NMR: δ = 138.9, 127.7 (2 C), 133.0 (2 C)] and finally a mixture of the starting material **12b** (6%) and 2,4-dibromo-3,5-dichloropyridine[27] (3%, m.p. 65−66 °C; ref.[27] 68.5−69.5 °C) which were identified by gas chromatography using authentic samples for comparison. Between these fractions the main product was collected in the form of white needles (2.5 g, 42%); m.p. 40−41 °C (ref.[28] 41−42 °C). − $^1$H NMR: δ = 8.28 (d, $J$ = 2.1 Hz, 1 H), 7.77 (d, $J$ = 2.1 Hz, 1 H). − $^{13}$C NMR: δ = 146.3, 139.3, 137.5, 133.7, 131.3. − $C_5H_2BrCl_2N$ (226.89): calcd. C 26.47, H 0.89; found C 26.46, H 0.88.

**Final Products: Pyridinecarboxylic Acids**

**2,3-Dichloro-4-pyridinecarboxylic Acid (1):** At −75 °C, diisopropylamine (3.5 mL, 2.5 g, 25 mmol) and 2,3-dichloropyridine (3.7 g, 25 mmol) were consecutively added to butyllithium (25 mmol) in tetrahydrofuran (50 mL) and hexanes (17 mL). After 2 h at −75 °C, the mixture was poured onto an excess of freshly crushed dry ice. Water was added (50 mL), the aqueous phase decanted and washed with diethyl ether (3 × 20 mL) before being acidified to pH 1 and extracted with diethyl ether. The combined organic layers were evaporated and the residue crystallized from ethanol; m.p. 195−197 °C; 4.6 g (96%). − $^1$H NMR: δ = 8.38 (d, $J$ = 5.0 Hz, 1 H), 7.59 (d, $J$ = 5.0 Hz, 1 H). − $^{13}$C NMR: δ = 165.6, 151.1, 146.9, 141.9, 128.4, 123.0. − $C_6H_3Cl_2NO_2$ (192.00): calcd. C 37.53, H 1.57; found C 37.86, H 1.52.

**2,4-Dichloro-3-pyridinecarboxylic Acid:** Prepared from 2,4-dichloropyridine (3.7 g, 25 mmol) and isolated as described in the preceding paragraph; colorless needles (4.2 g, 88%); m.p. 154−155 °C (from 75% aqueous methanol). − $^1$H NMR*: δ = 8.47 (d, $J$ = 5.4 Hz, 1 H), 7.75 (d, $J$ = 5.4 Hz, 1 H). − $^{13}$C NMR*: δ = 164.6, 151.1 (2 C), 141.5, 131.2, 124.6. − $C_6H_3Cl_2NO_2$ (192.00): calcd. C 37.53, H 1.57; found C 37.23, H 1.82.

**Methyl 4,5-Dichloro-3-pyridinecarboxylate (5b: $OCH_3$ instead of OH):** Prepared from 3,4-dichloropyridine (3.7 g, 25 mmol) in the same way as described for acid **1** (see above). The ethereal extract containing the 4,5-dichloro-3-pyridinecarboxylic acid (**5a**) was treated with ethereal diazomethane until the yellow color persisted. The solution was absorbed on silica gel (25 mL) and the powder, once dry, was poured on top of a chromatography column filled with more silica gel (125 mL) under hexanes. Elution with a 1:9 (v/v) mixture of ethyl acetate and hexanes gave white needles (3.3 g, 64%); m.p. 66−68 °C (after sublimation). − $^1$H NMR: δ = 8.87 (s, 1 H), 8.74 (s, 1 H), 3.98 (s, 3 H). − $^{13}$C NMR: δ = 163.8, 152.2, 149.5, 141.8, 132.5, 127.5, 53.1. − $C_7H_5Cl_2NO_2$ (206.03): calcd. C 40.81, H 2.45; found C 41.02, H 1.96.

**Methyl 3,4-Dichloro-2-pyridinecarboxylate (4b: $OCH_3$ instead of OH):** The same protocol as described for acid **1** was applied except that diisopropylamine was replaced by 2,2,6,6-tetramethylpiperidine (4.2 mL, 3.5 g, 25 mmol) and tetrahydrofuran by diethyl ether. This time both acids **4b** and **5b** formed in a 9:1 ratio. They were again converted into the methyl ester and the latter purified by chromatography as described in the preceding paragraph; white needles (2.7 g, 42%); m.p. 42−44 °C (after sublimation). − $^1$H NMR: δ = 8.45 (d, $J$ = 5.2 Hz, 1 H), 7.55 (d, $J$ = 5.2 Hz, 1 H), 4.01 (s, 3 H). − $^{13}$C NMR: δ = 164.4, 149.8, 147.3, 144.4, 129.5, 127.0, 53.3. − $C_7H_5Cl_2NO_2$ (206.03): calcd. C 40.81, H 2.45; found C 41.18, H 2.12.

**3,6-Dichloro-2-pyridinecarboxylic Acid (2):** At −75 °C, *tert*-butyllithium (25 mmol) in pentanes (17 mL) was added dropwise, in the course of 15 min., to a solution of 2,5-dichloropyridine (3.7 g, 25 mmol) in diethyl ether (50 mL). After 2 h at −75 °C, the mixture was poured onto dry ice. The acid formed was extracted as described above. Recrystallization from water gave a pure product (2.8 g, 58%); m.p. 149−151 °C (ref.[29] 150−152 °C). − $^1$H NMR: δ = 7.91 (d, $J$ = 8.5 Hz, 1 H), 7.55 (d, $J$ = 8.5 Hz, 1 H). − Trapping of the intermediate with *N*,*N*-dimethylformamide (1.8 mL, 1.5 g, 25 mmol) rather than with carbon dioxide gave **3,6-dichloro-2-pyridinecarbaldehyde** as white needles (3.5 g, 80%); m.p. 105−107 °C (from hexanes). − $^1$H NMR: δ = 10.2 (s, 1 H), 7.81 (d, $J$ = 8.5 Hz, 1 H), 7.49 (d, $J$ = 8.5 Hz, 1 H). − $^{13}$C NMR: δ = 188.5, 150.5, 147.3, 142.0, 131.9, 129.1. − $C_6H_3Cl_2NO$ (176.99): calcd. 40.95, H 1.72; found C 41.18, H 1.81.

**2,5-Dichloro-4-pyridinecarboxylic Acid (3):** At −75 °C, 2,5-dichloropyridine (3.7 g, 25 mmol) was added to a solution of butyllithium (25 mmol) and *N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine (5.3 mL, 4.3 g, 25 mmol) in tetrahydrofuran (50 mL) and hexanes (17 mL). After 2 h at −75 °C, the mixture was poured onto dry ice and the acid formed isolated by extraction as described above; m.p. 227−229 °C (from ethanol); 4.2 g (87%). − $^1$H NMR: δ = 8.47 (s, 1 H), 7.74 (s, 1 H). − $^{13}$C NMR: δ = 163.8, 149.9, 148.9, 140.1, 128.2, 124.3. − $C_6H_3Cl_2NO_2$ (192.00): calcd. C 37.53, H 1.57; found C 37.89, H 1.69.

**4,6-Dichloro-3-pyridinecarboxylic Acid (11):** At −75 °C, 2,4-dichloro-5-iodopyridine (**10**; 0.27 g, 1.0 mmol) was added to a solution of *tert*-butyllithium (2.0 mmol) in pentanes (1.5 mL) and diethyl ether (2.0 mL). After 15 min. at −75 °C, the mixture was poured onto an excess of freshly crushed dry ice. Water (5.0 mL) was added. The aqueous phase was washed with diethyl ether (2 × 5.0 mL), acidified to pH 1 and extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried and evaporated. Sublimation of the residue afforded colorless tufts (0.15 g, 79%); m.p. 151−152 (ref.[30] 152−153 °C). − $^1$H NMR: δ = 9.03 (s, 1 H), 7.53 (s, 1 H). − $^{13}$C NMR: δ = 166.8, 55.7, 153.2, 146.9, 126.4, 123.4.

**3,5-Dichloro-2-pyridinecarboxylic Acid (14):** Analogously as described in the preceding paragraph on a 25-fold increased scale

starting with 2-bromo-3,5-dichloropyridine (**13**); colorless needles (4.2 g, 88%); m.p. 151−152 °C. − $^1$H NMR: δ = 8.51 (d, *J* = 2.1 Hz, 1 H), 7.98 (d, *J* = 2.1 Hz, 1 H). − $^{13}$C NMR: δ = 165.0, 146.0, 145.7, 138.3, 134.0, 131.6. − $C_6H_3Cl_2NO_2$ (192.00): calcd. C 37.53, H 1.57; found C 37.61, H 1.59.

**2,6-Dichloro-4-pyridinecarboxylic Acid (17):** As described for the preparation of acid **14** from 2,6-dichloro-4-iodopyridine (**16**), again working on a 25 mmol scale but carrying out the reaction with *tert*-butyllithium (50 mmol) at −75 °C; m.p. 208−209 °C (ref.[29] 211 °C); 4.3 g (89%). − $^1$H NMR*: δ = 7.89 (s, 2 H). − $^{13}$C NMR*: δ =164.1, 150.5 (2 C), 145.0, 123.8 (2 C).

**2,4-Dichloro-5-iodo-3-pyridinecarboxylic Acid (18):** 2,4-Dichloro-3-iodopyridine (**9**, 1.4 g, 5 mmol) was treated with lithium diisopropylamide (5 mmol) in tetrahydrofuran (10 mL) as described above (see preparation of the isomer **10**), but the mixture was poured onto dry ice rather than being quenched with water. The acid was isolated by extraction first into the alkaline aqueous phase and then, after acidification, into dichloromethane (see above). 2,4-Dichloro-3-pyridinecarboxylic acid and 2,4-dichloro-5-iodo-3-pyridinecarboxylic acid (**18**) were isolated in a 2:3 ratio; 58%. Upon trituration with chloroform, the main component was obtained pure (0.4 g, 25%); m.p. 202−203 °C. − $^1$H NMR: δ = 8.72 (s, 1 H). − $^{13}$C NMR: δ = 164.7, 156.7, 149.5, 147.6, 131.8, 96.5. − $C_6H_2Cl_2INO_2$ (317.90): calcd. C 22.67, H 0.63; found C 22.64, H 0.88.

**2,6-Dichloro-4-iodo-3-pyridinecarboxylic Acid (20):** As described in the preceding paragraph, 2,6-dichloro-3-iodopyridine (2.7 g, 10 mmol) was converted into the acid **20**, which was purified by trituration with chloroform (15 mL) and sublimation; m.p. 227−228 °C (decomp.); 1.8 g (57%). − $^1$H NMR (D3CCOCD3): δ = 8.11 (s, 1 H). − $^{13}$C NMR: δ = 166.2, 150.8, 145.5, 137.0, 134.1, 107.4. − $C_6H_2Cl_2INO_2$ (317.90): calcd. C 22.67, H 0.63; found C 22.28, H 0.97.

**2-Bromo-3,5-dichloro-4-pyridinecarboxylic Acid (19):** In the same manner, acid **19** was obtained from 4-bromo-3,5-dichloropyridine (2.3 g, 10 mmol). Extraction, trituration and sublimation again afforded an analytically pure product as colorless tufts (1.1 g, 41%); m.p. 200−202 °C. − $^1$H NMR: δ = 8.56 (s, 1 H). − $^{13}$C NMR: δ = 163.2, 15.9, 148.4, 143.7, 140.8, 128.1. − $C_6H_2Br_2NO_2$ (270.90): calcd. C 26.60, H 0.74; found C 27.04, H 0.39.

**Miscellaneous: Formylation and Oxidation Products**

**3,6-Dichloro-2-pyridinecarbaldehyde (6):** A solution of 2,5-dichloropyridine (3.7 g, 25 mmol) and *tert*-butyllithium (25 mmol) in diethyl ether (50 mL) and pentanes (15 mL) was kept 6 h at −100 °C before *N*,*N*-dimethylformamide (1.8 mL, 1.5 g, 25 mmol) was added. After 30 min. at −100 °C and 30 min. at −75 °C, the mixture was poured into water (50 mL), washed with diethyl ether (2 × 20 mL), acidified to pH 2 and extracted with diethyl ether (3 × 20 mL). After evaporation of the combined organic layers and recrystallization from hexanes, white needles were obtained (3.5 g, 80%); m.p. 105−107 °C. − $^1$H NMR: δ = 10.20 (s, 1 H), 7.81 (d, *J* = 8.5 Hz, 1 H), 7.49 (d, *J* = 8.5 Hz, 1 H). − $^{13}$C NMR: δ = 188.5, 150.0, 147.3, 142.0, 131.9, 129.1. − $C_6H_3Cl_2NO$ (176.00): calcd. C 40.95, H 1.72; found C 41.18, H 1.82.

**2,5-Dichloro-4(1*H*)pyridinone (7):** At −75 °C, 2,5-dichloropyridine (7.4 g, 50 mmol) was added to a solution of butyllithium (50 mmol) and *N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine (10 mL, 8.7 g, 50 mmol) in tetrahydrofuran (70 mL) and hexanes (30 mL). After 2 h at −75 °C, the mixture was treated with fluorodimethoxyborane−diethyl ether[7,32] (9.3 mL, 8.3 g, 50 mmol) and at 0 °C with 35% aqueous hydrogen peroxide (50 mL, 57 g, 60 mmol) and a 3.0 M aqueous solution (25 mL) of sodium hydroxide. The two-phase mixture was vigorously stirred for 2 h at 25 °C. The aqueous layer was decanted and washed with diethyl ether (3 × 50 mL). The organic solvent was evaporated and the residue crystallized from 75% aqueous ethanol affording colorless needles (7.6 g, 69%); m.p. 192−194 °C. − $^1$H NMR*: δ = 8.27 (s, 1 H), 6.95 (s, 1 H). − $^{13}$C NMR*: δ = 161.6, 149.0, 128.0, 118.6, 111.3. − $C_5H_3Cl_2NO$ (163.99): calcd. C 36.62, H 1.84; found C 36.62, H 2.03.

**3,6-Dichloro-4(1*H*)pyridinone-2-carboxylic Acid (8):** At −75 °C, *tert*-butyllithium (50 mmol) in pentanes (30 mL) was added to a solution of 2,5-dichloro-4(1*H*)pyridinone (**7**; 4.1 g, 25 mmol) in tetrahydrofuran (90 mL). After 2 h at −75 °C, the mixture was poured on an excess of freshly crushed dry ice. The solid remaining after the evaporation of the volatiles was taken up in water (100 mL). The aqueous phase was washed with diethyl ether (3 × 25 mL), acidified to pH 1 and extracted with diethyl ether (3 × 50 mL). After evaporation of the organic solvent, the residue was crystallized from 70% aqueous methanol to give colorless needles (3.0 g, 58%); m.p. 173−175 °C (decomp.). − $^1$H NMR: δ = 7.03 (1 H). − $^{13}$C NMR: δ = 165.1, 163.0, 148.8, 148.4, 118.2, 113.2. − $C_7H_3Cl_2NO_3$ (208.00): calcd. C 34.65, H 1.45; found C 34.60, H 1.48.

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