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Logistic flexibility in the preparation of isomeric halopyridinecarboxylic acids

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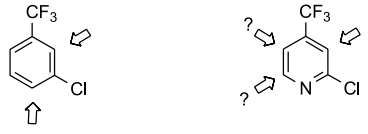
Abstract—Although there are many conceivable ways to funtionalize, and specifically carboxylate, 2-chloro-4-(trifluoromethyl)pyridine optionally at all three vacant positions, it is more straightforward to prepare only the 2-chloro-4-(trifluoromethyl)pyridine-3-carboxylic acid (**1**) from this precursor and the other 6-chloro-4-(trifluoromethyl)pyridine-2- and -3-carboxylic acids (**2** and **3**) from a different one, viz. 5-bromo-2-chloro-4-(trifluoromethyl)pyridine. In the same manner, it proved more convenient to convert 5-chloro-2-(trifluoromethyl)pyridine in only two of the corresponding acids (**6** and **7**) and to make the third one (**8**) from 3-bromo-5-chloro-2-(trifluoromethyl)pyridine as an alternative starting material. All model substrates for functionalization were readily accessible from the correspondingly substituted chloroiodopyridine through heavy halogen displacement by in situ generated (trifluoromethyl)copper.

1. Introduction

The principle of regioexhaustive functionalization[1] was successfully applied to several chloro(trifluoromethyl)pyridines and one bromo(trifluoromethyl)pyridine as disclosed in preceding articles.[2,3] Relying on procedures such as reagent-modulated site selective metalation, regiocontrol through protective groups and deprotonation-triggered heavy halogen migrations, metals were optionally introduced into any vacant position of each substrate and the organometallic species thus produced were trapped with a suitable electrophile, typically with carbon dioxide. The present report is a plea to prove pragmatism while pursuing the goal of developing a given model structure into all regioisomerically possible derivatives. Although it looks logistically most attractive to have the same building block as the common precursor to all congeners, it may sometimes be more advantageous to employ two or even three different starting materials. The correctness of this assertion will be illustrated by the synthesis of two 'triplets' of regioisomeric chloro(trifluoromethyl)pyridinecarboxylic acids.

2. Results

2-Chloro-4-(trifluoromethyl)pyridine is a commercial compound, but its catalogue price is prohibitive (about 20,000 €/mol). Therefore, we have made it from the known 2-chloro-4-iodopyridine by heavy halogen displacement with in situ generated (trifluoromethyl)copper.[4] Depending on the choice of the reagent, 1-chloro-3-(trifluoromethyl)-benzene undergoes a permutational hydrogen/metal interconversion ('metalation') either at the 2- or 6-position.[5] Seen against this background, one would expect 2-chloro-4-(trifluoromethyl)pyridine to react with bases preferentially or exclusively at the 3-position. Other sites would be attacked only under exceptional conditions, if at all.



In fact, the metalation of 2-chloro-4-(trifluoromethyl)pyridine proceeded smoothly at the 3-position when accomplished with lithium diisopropylamide in tetrahydrofuran at −75 °C. Reaction with dry ice afforded the 2-chloro-4-(trifluoromethyl)pyridine-3-carboxylic acid (**1**) in 82% yield. In contrast, no trace of the isomeric pyridinecarboxylic acids **2** and **3**, respectively, was identified in the product mixture when other metalating reagents, such as Caubère's base, that is, butyllithium in the presence

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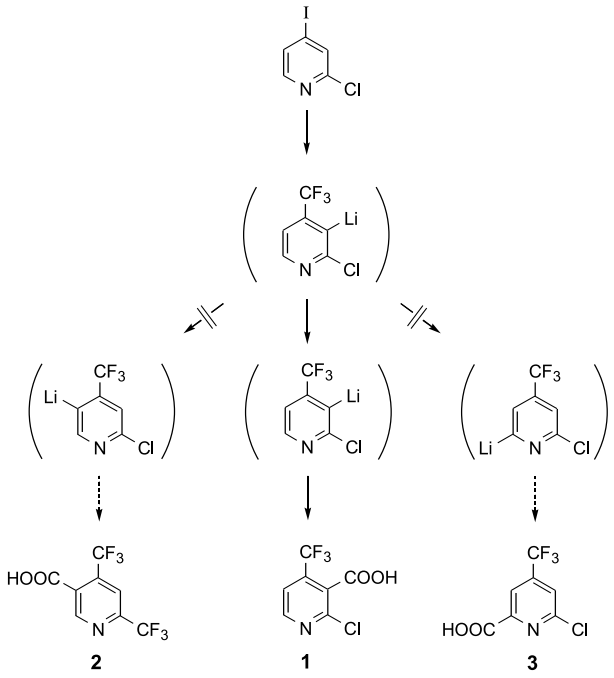
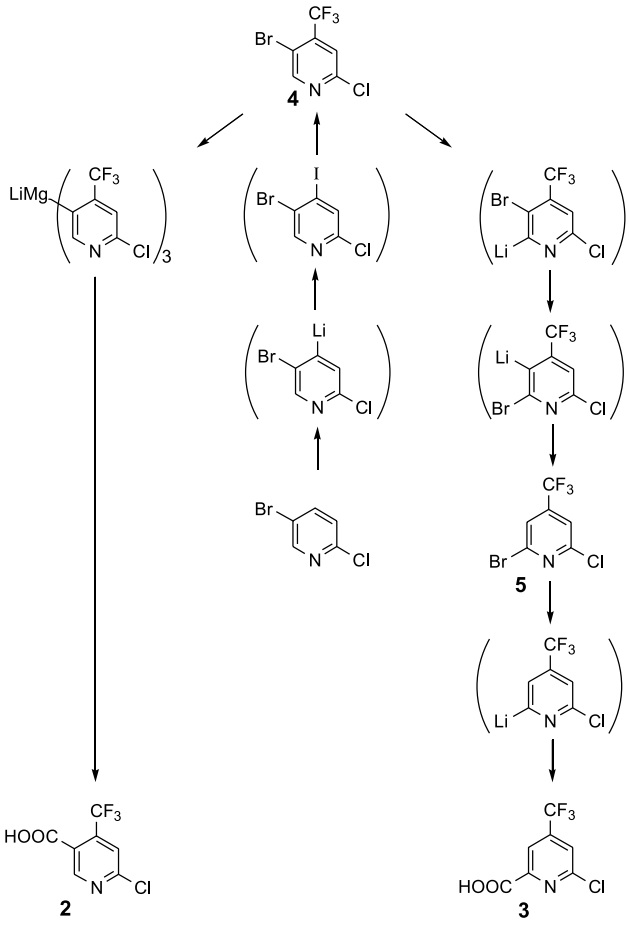


Scheme 1.

of lithium 2-(dimethylamino)ethoxide,[6] were employed (Scheme 1).

Both acids **2** and **3** were found to be readily accessible through 5-bromo-2-chloro-4-(trifluoromethyl)pyridine (**4**). Consecutive treatment of 5-bromo-2-chloropyridine with lithium diisopropylamide and molecular iodine afforded 5-bromo-2-chloro-4-iodopyridine (66%) from which the heaviest halogen was readily displaced by the trifluoromethyl entity. When the resulting bromopyridine **4** (64%) was subjected to a halogen/metal permutation with lithium tributylmagnesate,[7,8] the 2-chloro-4-(trifluoromethyl)pyridine-5-carboxylic acid (**2**; 77%) was obtained after carboxylation. On the other hand, when intermediate **4** was exposed to lithium disopropylamide, a basicity gradient driven heavy halogen migration[9,10] was unleashed which provided 2-bromo-6-chloro-4-(trifluoromethyl)pyridine (**5**; 68%) after neutralization. This time, the halogen/metal permutation was accomplished with butyllithium in toluene at −75 °C. The resulting organometallic species was carboxylated to give the 6-chloro-4-(trifluoromethyl)pyridine-2-carboxylic acid (**3**; 82%) (Scheme 2).

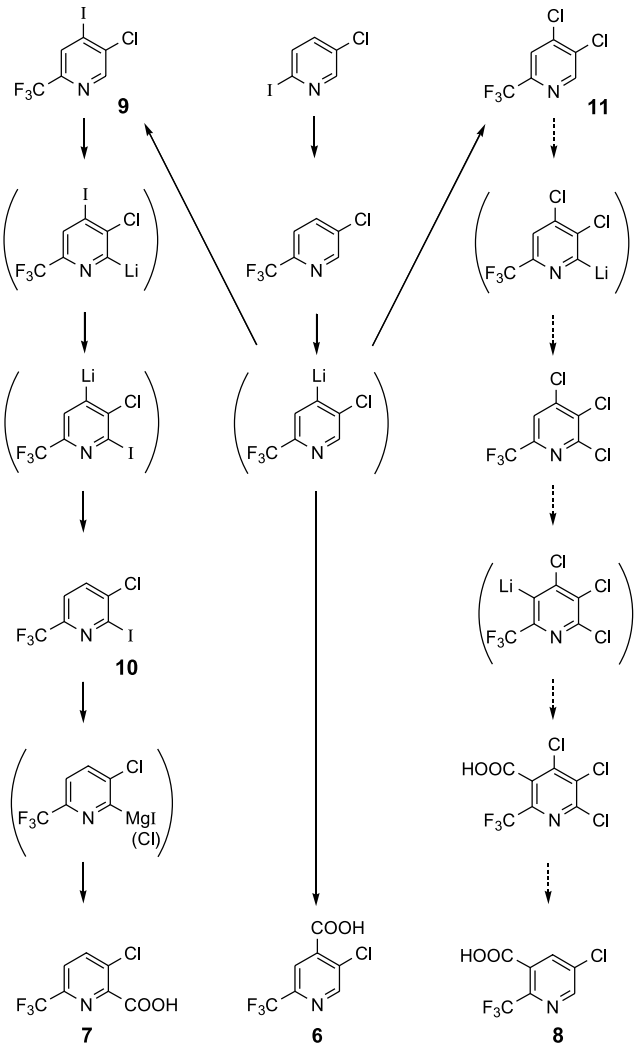


Scheme 2.

1-Chloro-4-(trifluoromethyl)benzene is invariably metalated at the 2-position. This allows us to predict the deprotonation of 5-chloro-2-(trifluoromethyl)pyridine to occur essentially at the 4-position as the intrinsic local acidity in pyridines increases with the distance of the CH bond from the heterocyclic nitrogen atom.[11,12] On the other hand, the coordination-requiring mixture of butyllithium with 2-(dimethylamino)ethoxide might at least this time favor the attack at the 2-position (in analogy with the behavior of 3-chloropyridine[13]).

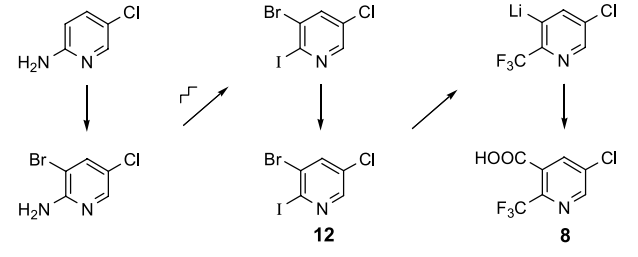
In fact, consecutive treatment of 5-chloro-2-(trifluoromethyl)pyridine with an excess of Caubère's base and dry ice afforded 3-chloro-6-(trifluoromethyl)pyridine-2-carboxylic acid (**7**) in 40% yield. The same acid was prepared in 95% yield from 3-chloro-2-iodo-6-(trifluoromethyl)pyridine (**10**) by consecutive reaction with isopropylmagnesium chloride and dry ice. The iodo compound **10** resulted from the lithium diisopropylamide-triggered isomerization of 5-chloro-4-iodo-2-(trifluoromethyl)pyridine (**9**), which was obtained by the interception of 4-lithiated 5-chloro-2-(trifluoromethyl)pyridine with elemental iodine in 86% yield. Carboxylation of the same intermediate furnished the 5-chloro-2-(trifluoromethyl)pyridine-4-carboxylic acid (**6**; 83%) (Scheme 3).

4,5-Dichloro-2-(trifluoromethyl)pyridine (**11**), prepared by reaction of the 4-lithiated 5-chloro-2-(trifluoromethyl)pyridine with 1,1,2-trichloro-1,2,2-trifluoroethane in 48% yield, and 2,3,4-trichloro-5-(trifluoromethyl)pyridine were the milestones on the initially conceived route to 5-chloro-2-(trifluoromethyl)pyridine-3-carboxylic acid (**8**). To remove the extra chloro substituents at the nucleophilically activated 2- and 4-positions, one could have replaced one after the other of them by a hydrazino unit and eventually carried out oxidative dediazotations.[14,15] Ultimately, this sequence was considered too laborious as it would have comprised at least half a dozen of operational steps. Therefore, we elaborated a short-cut approach starting



Scheme 3.

with the inexpensive 2-amino-5-chloropyridine which was brominated, diazotized, bromodediazotized, subjected to iodine/bromine displacement and converted into 3-bromo-5-chloro-2-(trifluoromethyl)pyridine (**12**) by CF_3I displacement. Halogen/metal permutation using lithium tributylmagnesate and reaction with carbon dioxide completed the preparation of 5-chloro-2-(trifluoromethyl)pyridine-3-carboxylic acid (**8**; 84%) (Scheme 4).



Scheme 4.

The chloro(trifluoromethyl)pyridinecarboxylic acids described above will certainly find their place in the life science arena as attractive building blocks. In addition, their reactivity profile can be profoundly modified by the nucleophilic displacement of the chlorine atom if located at the 2-, 4- or 6-position. Thus, both 2-chloro-4-(trifluoromethyl)pyridine-3-carboxylic acid (**1**) and 2-chloro-5-(trifluoromethyl)pyridine-4-carboxylic acid[2] were readily converted under evolution of hydrogen chloride into the bromo analogs 2-bromo-4-(trifluoromethyl)pyridine-3-carboxylic acid (80%) and 2-bromo-5-(trifluoromethyl)pyridine-4-carboxylic acid (84%), respectively, when treated with bromotrimethylsilane at 100 °C.

3. Experimental

3.1. Generalities

Working practices and abbreviations are specified in previous articles from this laboratory.[16–18] ^1H and (^1H decoupled) ^{13}C NMR spectra were recorded of samples dissolved in deuterochloroform at 400 and 101 MHz, respectively, relative to the internal standard tetramethylsilane (chemical shift $\delta=0.00$ ppm). The samples were dissolved in deuterochloroform or, if marked by an asterisk, in hexadeuteroacetone unless stated otherwise.

3.2. Starting materials

5-Bromo-2-chloropyridine was prepared by the diazotation of the commercially available 2-amino-5-bromopyridine essentially as described in the literature[19] but in the absence of cuprous chloride (as this has no effect on the rate of the reaction nor on the yield). 2-Amino-3-bromo-5-chloropyridine[20] could probably be directly converted into the required 3-bromo-5-chloro-2-iodopyridine but existing methods of diazotation seemed either complicated or low yielding.[21,22] Therefore, we have preferred the detour through the 2,3-dibromo-5-chloropyridine (see below).

3.2.1. 5-Bromo-4-iodo-2-chloropyridine. A solution of 5-bromo-2-chloropyridine (38 g, 0.20 mol) in tetrahydrofuran (0.20 L) was added dropwise over 1 h to the solution prepared from diisopropylamine (28 mL, 20 g, 0.20 mol) and butyllithium (0.20 mol) in tetrahydrofuran (0.27 L) and hexanes (0.12 L) kept in a dry ice/methanol bath. Afterwards, the reaction mixture was kept 45 min at −75 °C, before iodine (51 g, 0.20 mol) dissolved in tetrahydrofuran (0.15 L) was added in one shot. At 25 °C, the reaction mixture was filtered through basic alumina (0.10 L) and eluted with diethyl ether (2×0.20 L). After evaporation of the volatiles, the residue crystallized from ethanol as colorless needles; mp 144–145 °C; yield: 42.0 g (66%). ^1H NMR: $\delta=8.47$ (s, 1H), 7.86 (s, 1H). ^{13}C NMR: $\delta=149.8$, 149.6, 134.8, 127.4, 114.1. Anal. Calcd for $C_5H_2BrClIN$ (318.34): C 18.87, H 0.63. Found: C 18.83, H 0.69.

3.2.2. 5-Bromo-2-chloro-4-(trifluoromethyl)pyridine (4). 'Spray dried' potassium fluoride (6.4 g, 0.11 mol) and cuprous iodide (21 g, 0.11 mol) were thoroughly mixed before being heated under vacuum (1 mm Hg) with the flame of a Bunsen burner with gentle shaking until an homogeneous greenish color was obtained. *N*-Methylpyrrolidinone (0.20 L), trimethyl(trifluoromethyl)silane (15 mL, 14 g, 0.10 mol) and, after the slurry had been slowly heated

to 50 °C in the course of 45 min, 5-bromo-2-chloro-4-iodopyridine (32 g, 0.10 mol) were added. After 20 h at 50 °C, the reaction mixture was poured into 12% aqueous ammonia (0.20 L) and extracted with diethyl ether (3× 0.20 L). The combined organic layers were washed with 12% aqueous ammonia (2×0.20 L), 2.0 M hydrochloric acid (0.10 L), a saturated solution (0.10 L) of aqueous sodium hydrogen carbonate and brine (0.10 L). After drying and upon distillation, a colorless oil was collected; bp 80–81 °C/16 mm Hg; mp 11–13 °C; n_D^{20} 1.5084; d_4^{20} 1.813; yield: 18.3 g (64%). ^{1}H NMR: δ=8.68 (s, 1H), 7.62 (s, 1H). ^{13}C NMR: δ=153.9, 151.2, 140.0 (q, J=33 Hz), 122.6 (q, J=5 Hz), 121.0 (q, J=275 Hz), 115.8 (q, J=2 Hz). Anal. Calcd for $C_6H_2BrClF_3N$ (260.44): C 27.67, H 0.77. Found: C 27.75, H 0.56.

3.2.3. 2-Bromo-6-chloro-4-(trifluoromethyl)pyridine (5). 5-Bromo-2-chloro-4-(trifluoromethyl)pyridine (2.9 mL, 5.2 g, 20 mmol) was added to the solution prepared at 0 °C from 2,2,6,6-tetramethylpiperidine (6.8 mL, 5.7 g, 40 mmol) and butyllithium (40 mmol) in diethyl ether (0.10 L) and hexanes (25 mL) kept in a dry ice/methanol bath. After 2 h at −75 °C, the mixture was treated with 1.0 M hydrochloric acid (50 mL). The organic layer was filtered through a pad of basic alumina (50 mL) which was rinsed with diethyl ether (0.10 L). Upon distillation, a colorless oil was obtained; bp 68–70 °C/12 mm Hg; n_D^{20} 1.4966; d_4^{20} 1.770; yield: 3.52 g (68%). ^{1}H NMR: δ=7.66 (s, 1H), 7.53 (s, 1H). ^{13}C NMR: δ=152.4, 142.6 (q, J=33 Hz), 141.7, 122.9 (q, J=4 Hz), 121.2 (q, J=274 Hz), 119.5 (q, J=4 Hz). Anal. Calcd for $C_6H_2BrClF_3N$ (260.44): C 27.67, H 0.77. Found: C 27.75, H 0.75.

3.2.4. 5-Chloro-2-iodopyridine. 2-Bromo-5-chloropyridine[23] (9.6 g, 50 mmol) was heated to reflux in the presence of sodium iodide (22 g, 0.15 mol) and chlorotrimethylsilane (6.4 mL, 5.4 g, 50 mmol) in propionitrile for 6 h. The reaction mixture was poured into 2.0 M aqueous solution of sodium hydroxide and extracted with diethyl ether (2× 50 mL). The combined organic layers were washed with brine (50 mL), dried and evaporated. The residue crystallized from hexanes as colorless platelets; mp 85–87 °C (lit.[23] mp 85–87 °C); yield: 10.4 g (87%; lit.[23] 52% from the 2,5-dichloropyridine).

3.2.5. 5-Chloro-2-(trifluoromethyl)pyridine. Analogously from 5-chloro-2-iodopyridine (24 g, 0.10 mol), a colorless solid was obtained after sublimation of the reaction product; mp 37–39 °C; 13.1 g (72%). ^{1}H NMR: δ=8.69 (d, J=2.3 Hz, 1H), 7.87 (dd, J=8.3, 2.3 Hz, 1H), 7.66 (d, J=8.3 Hz, 1H). ^{13}C NMR: δ=149.0, 146.2 (q, J=35 Hz), 137.0, 135.2, 121.3 (q, J=2 Hz), 121.2 (q, J=274 Hz). Anal. Calcd for $C_6H_3ClF_3N$ (181.54): C 39.70, H 1.67. Found: C 39.66, H 1.60.

3.2.6. 5-Chloro-4-iodo-2-(trifluoromethyl)pyridine (9). 5-Chloro-2-(trifluoromethyl)pyridine (3.6 g, 50 mmol) was added to the solution prepared from butyllithium (20 mmol) and diisopropylamine (2.8 mL, 2.0 g, 20 mmol) in tetrahydrofuran (30 mL) and hexanes (13 mL) kept in a dry ice/methanol bath. After 2 h at −75 °C, the mixture was treated with iodine (5.1 g, 20 mmol) in tetrahydrofuran (20 mL). The solvents were evaporated and the residue partitioned between diethyl ether (20 mL) and a 2.0 M aqueous solution of sodium thiosulfate (20 mL). The phases were separated and the aqueous one extracted with diethyl ether (20 mL). The combined organic layers were washed with 2.0 M hydrochloric acid (20 mL), saturated sodium hydrogen carbonate aqueous solution, dried and evaporated. The residue crystallized from hexanes as yellow needles; 5.35 g (87%); mp 83–85 °C. ^{1}H NMR: δ=8.63 (s, 1H), 8.15 (s, 1H). ^{13}C NMR: δ=148.3, 146.0 (q, J=35 Hz), 140.4, 131.8, 120.2 (q, J=275 Hz). Anal. Calcd for $C_6H_2ClF_3IN$ (307.44): C 23.44, H 0.65. Found: C 23.16, H 0.78.

3.2.7. 2-Iodo-3-chloro-6-(trifluoromethyl)pyridine (10). 5-Chloro-4-iodo-2-(trifluoromethyl)pyridine (1.5 g, 5.0 mmol) was added to the solution prepared from butyllithium (5.0 mmol) and diisopropylamine (0.71 mL, 0.51 g, 5.0 mmol) in tetrahydrofuran (20 mL) and hexanes (3 mL) kept in a dry ice/methanol bath. After 2 h at −75 °C, the mixture was treated with water (2.0 mL) and the solvents were evaporated. The residue was taken up in diethyl ether (30 mL) and was washed with 2.0 M hydrochloric acid (20 mL) and saturated sodium hydrogen carbonate aqueous solution. After evaporation, the residue crystallized from hexanes as yellowish prisms; 1.27 g (83%); mp 62–64 °C. ^{1}H NMR: δ=7.81 (dq, J=8.0, 0.6 Hz, 1H), 7.60 (d, J=8.0 Hz, 1H). ^{13}C NMR: δ=146.5 (q, J=36 Hz), 141.8, 136.9, 121.6, 120.4 (q, J=3 Hz), 120.3 (q, J=275 Hz). Anal. Calcd for $C_6H_2ClF_3IN$ (307.44): C 23.44, H 0.65. Found: C 23.53, H 0.65.

3.2.8. 2,3-Dibromo-5-chloropyridine. At 60 °C, 2-amino-3-bromo-5-chloropyridine[20] (73 g, 0.35 mol) was dissolved in 48% hydrobromic acid (0.20 L, 0.30 kg, 1.8 mol). After cooling to −5 °C, bromine (36 mL, 0.11 kg, 0.70 mol) was added dropwise over 20 min. A solution of sodium nitrite (60 g, 0.90 mol) in water (80 mL) was then added at a rate to keep the temperature of the reaction mixture between −5 and 0 °C. When finished, the temperature was allowed to reach 25 °C. The bromine was reduced with an excess of solid sodium sulfite, and the reaction mixture was extracted with diethyl ether (3×0.20 L). The combined organic layers were filtered through a pad of basic alumina (0.25 L) which was rinsed with diethyl ether (0.40 L). Evaporation of the volatiles afforded pure 2,3-dibromo-5-chloropyridine; mp 38–41 °C (lit.[24] mp 39.5–43.0 °C); yield: 64.9 g (68%).

3.2.9. 3-Bromo-5-chloro-2-iodopyridine. A mixture of 2,3-dibromo-5-chloropyridine (20 g, 75 mmol), sodium iodide (33 g, 0.22 mol) and chlorotrimethylsilane (9.5 mL, 8.1 g, 75 mmol) in propionitrile (75 mL) was heated under reflux for 45 min. The reaction mixture was then poured into a 2.0 M aqueous solution of sodium hydroxide (0.20 L) and extracted with diethyl ether (3×0.20 L). The combined organic layers were washed with brine and evaporated to yield some 20 g of a brownish oil containing 2-iodo-3-bromo-5-chloropyridine (79%) and 3-bromo-5-chloropyridine (21%) as determined by gas chromatography (DB-1, 20 m, 150 °C, pentadecane as an internal standard). Twofold crystallization from methanol afforded pure 3-bromo-5-chloro-2-iodopyridine as tiny colorless needles; mp 58–60 °C; yield: 9.7 g (42%). ^{1}H NMR: δ=8.30 (d, J=2.2 Hz, 1H), 7.83 (d, J=2.2 Hz, 1H). ^{13}C NMR: δ=147.2, 139.1, 131.9, 130.0, 120.7. Anal. Calcd for $C_5H_2BrClIN$ (318.34):

C 18.87, H 0.63. Found: C 18.88, H 0.62. Threefold crystallization of the mother liquors from methanol afforded pure 3-bromo-5-chloropyridine as colorless platelets; mp 74–76 °C; 0.81 g (6%). ^{1}H NMR: δ=8.57 (d, J=1.9 Hz, 1H), 8.51 (d, J=2.2 Hz, 1H), 7.87 (t, J=2.1 Hz, 1H). ^{13}C NMR: δ=148.8, 147.0, 138.3, 132.4, 120.5. Anal. Calcd for C_5H_3BrClN (192.44): C 31.21, H 1.57. Found: C 31.27, H 1.16.

3.2.10. 4,5-Dichloro-2-(trifluoromethyl)pyridine (11). 5-Chloro-2-(trifluoromethyl)pyridine (5.4 g, 30 mmol) was added to the solution prepared from diisopropylamine (4.2 mL, 3.0 g, 30 mmol) and butyllithium (30 mmol) in tetrahydrofuran (45 mL) and hexanes (12 mL) kept in a dry ice/methanol bath. After 45 min at −75 °C, 1,2,2-trichloro-1,2,2-trifluoroethane (3.6 mL, 5.6 g, 30 mmol) was added and the reaction mixture was allowed to reach 25 °C. After dilution with diethyl ether (30 mL), the reaction mixture was washed consecutively with 2.0 M hydrochloric acid (2×20 mL), a saturated aqueous solution (20 mL) of sodium hydrogen carbonate and brine (20 mL). Upon distillation, a slightly yellowish oil was obtained; bp 65–66 °C/19 mm Hg; mp 10–13 °C; n_D^{20} 1.4732; d_4^{20} 1.549; yield: 3.12 g (48%); ^{1}H NMR: δ=8.73 (s, 1H), 7.79 (s, 1H). ^{13}C NMR: δ=150.5, 147.1 (q, J=35 Hz), 143.6, 134.0, 122.5 (q, J=3 Hz), 120.7 (q, J=275 Hz). Anal. Calcd for $C_6H_2Cl_2F_3N$ (215.99): C 33.36, H 0.93. Found: C 33.54, H 1.04.

3.2.11. 3-Bromo-5-chloro-2-(trifluoromethyl)pyridine (12). A similar reaction as the one described above (see preparation of 5-bromo-2-chloro-4-(trifluoromethyl)pyridine; subsection 3.2.2) was performed with 3-bromo-5-chloro-2-iodopyridine (32 g, 0.10 mol); upon distillation, a colorless oil was obtained which solidified; bp 75–76 °C/13 mm Hg; mp 23–25 °C; yield: 18.0 g (69%). ^{1}H NMR: δ=8.58 (d, J=1.9 Hz, 1H), 8.09 (d, J=1.9 Hz, 1H). ^{13}C NMR: δ=146.2, 144.3 (q, J=35 Hz), 142.2, 135.2, 120.9 (q, J=275 Hz), 118.3. Anal. Calcd for $C_6H_2BrClF_3N$ (260.44): C 27.67, H 0.77. Found: C 27.30, H 0.47.

3.3. Carboxylic acids derived from 2-chloro-4-(trifluoromethyl)pyridine

3.3.1. 2-Chloro-4-(trifluoromethyl)pyridine-3-carboxylic acid (1). 2-Chloro-4-(trifluoromethyl)pyridine (6.4 mL, 9.1 g, 50 mmol) was added to the solution prepared from diisopropylamine (7.0 mL, 5.1 g, 50 mmol) and butyllithium (50 mmol) in tetrahydrofuran (0.17 L) and hexanes (23 mL) kept in a dry ice/methanol bath. After 2 h at −75 °C, the reaction mixture was poured onto an excess of freshly crushed dry ice covered with tetrahydrofuran (25 mL) before being allowed to reach 25 °C. Upon extraction with 2.0 M aqueous solution of sodium hydroxide (3×50 mL), washing of the combined basic organic layers with diethyl ether (2×50 mL), acidification to pH 1 with concentrated hydrochloric acid, extraction with diethyl ether (3×0.10 mL), drying and evaporation to dryness, a pale brown residue was obtained. Crystallization of the latter from ethyl acetate afforded colorless prisms; mp 150–151 °C; 9.31 g (82%). ^{1}H NMR: δ=8.62 (d, J=5.2 Hz, 1H), 7.54 (d, J=5.2 Hz, 1H). ^{13}C NMR: δ=165.4, 150.5, 148.9, 137.4 (q, J=35 Hz), 124.4, 121.7 (q, J=275 Hz), 118.8 (q, J=4 Hz). Anal. Calcd for $C_6H_3ClF_3NO_2$ (225.55): C 37.28, H 1.34. Found: C 37.21, H 1.32.

3.3.2. 6-Chloro-4-(trifluoromethyl)pyridine-3-carboxylic acid (2). At 0 °C, butylmagnesium chloride (6.6 mmol) in tetrahydrofuran (4.2 mL) was added to butyllithium (13 mmol) in hexanes (8.5 mL). After 10 min, the reaction mixture was diluted with tetrahydrofuran (25 mL), cooled to −75 °C. 5-Bromo-2-chloro-4-(trifluoromethyl)pyridine (2.9 mL, 5.2 g, 20 mmol) was added and the reaction mixture was kept 45 min at −75 °C, before being poured onto an excess of freshly crushed dry ice covered with tetrahydrofuran (25 mL). The solvents were evaporated, and the residue partitioned between 6.0 M hydrochloric acid (20 mL) and diethyl ether (70 mL). The organic phase was dried, evaporated and the residue crystallized from heptane as colorless needles; mp 114–116 °C; yield: 3.49 g (77%). ^{1}H NMR: δ=9.13 (s, 1H), 7.77 (s, 1H). ^{13}C NMR: δ=168.1, 156.6, 153.0, 140.2 (q, J=35 Hz), 122.8 (q, J=2 Hz), 122.1 (q, J=6 Hz), 121.1 (q, J=275 Hz). Anal. Calcd for $C_7H_3ClF_3NO_2$ (225.55): C 37.28, H 1.34. Found: C 37.55, H 1.09.

3.3.3. 6-Chloro-4-(trifluoromethyl)pyridine-2-carboxylic acid (3). 2-Bromo-6-chloro-4-(trifluoromethyl)pyridine (1.5 mL, 2.6 g, 10 mmol) was added to a solution of butyllithium (10 mmol) in toluene (50 mL) and hexanes (6.1 mL) kept in a dry ice/methanol bath. After 15 min at −75 °C, the reaction mixture was poured onto an excess of freshly crushed dry ice covered with diethyl ether (25 mL). At 25 °C, the products were partitioned between diethyl ether (20 mL) and 6.0 M hydrochloric acid (20 mL). The organic layer was dried and the volatiles evaporated. Crystallization of the residue from petroleum ether afforded tiny colorless needles; mp 99–101 °C; yield: 1.85 g (82%). ^{1}H NMR: δ=8.38 (s, 1H), 7.85 (s, 1H). ^{13}C NMR: δ=164.1, 152.4, 148.4, 143.1 (q, J=36 Hz), 125.0 (q, J=4 Hz), 121.5 (q, J=274 Hz), 119.6 (q, J=3 Hz). Anal. Calcd for $C_7H_3ClF_3NO_2$ (225.55): C 37.28, H 1.34. Found: C 37.14, H 1.30.

3.4. Carboxylic acids derived from 5-chloro-2-(trifluoromethyl)pyridine

3.4.1. 5-Chloro-2-(trifluoromethyl)pyridine-4-carboxylic acid (6). 5-Chloro-2-(trifluoromethyl)pyridine (1.8 g, 10 mmol) was added to the solution prepared from diisopropylamine (1.4 mL, 1.0 g, 10 mmol) and butyllithium (10 mmol) in tetrahydrofuran (15 mL) and hexanes (5 mL) kept in a dry ice/methanol bath. After 45 min at −75 °C, the mixture was poured on an excess of freshly crushed dry ice. Volatiles were then evaporated and the residue crystallized from a 9:1 (v/v) mixture of 2.0 M aqueous solution of hydrochloric acid and ethanol as colorless needles; mp 206–207 °C (reprod.); 1.88 g (83%). ^{1}H NMR*: δ=8.94 (s, 1H), 8.22 (s, 1H). ^{13}C NMR*: δ=152.7, 147.1 (q, J=35 Hz), 140.3, 134.0, 122.3 (q, J=2 Hz), 122.3 (q, J=273 Hz). Anal. Calcd for $C_7H_3ClF_3NO_2$ (225.55): C 37.27, H 1.34; found C 36.97, H 1.35.

3.4.2. 3-Chloro-6-(trifluoromethyl)pyridine-2-carboxylic acid (7). Isopropylmagnesium chloride (3.0 mmol) was added to 3-chloro-2-iodo-6-(trifluoromethyl)pyridine

(0.92 g, 3.0 mmol) in tetrahydrofuran (6 mL) at −75 °C. After 2 h, carbon dioxide was bubbled through the solution for 20 min, before adding diethyl ether (20 mL) and 6.0 M hydrochloric acid (10 mL). The phases were separated, and the aqueous layer extracted with diethyl ether (10 mL). The combined organic layers were dried and evaporated. Sublimation of the residue afforded a colorless solid; mp 97–99 °C (colorless needles from ethyl acetate/hexanes 1:6); 0.642 g (95%). ^{1}H NMR: δ=8.17 (dq, J=8.6, 0.7 Hz, 1H), 7.90 (d, J=8.6 Hz, 1H). ^{13}C NMR: δ=161.7, 145.1 (q, J=37 Hz), 143.3, 142.7, 136.4, 124.8 (q, J=2 Hz), 120.8 (q, J=275 Hz). Anal. Calcd for $C_6H_3ClF_3NO_2$ (225.55): C 37.27, H 1.34. Found: C 37.46, H 1.24. The same acid was obtained in 40% yield (0.90 g) after treatment of 5-chloro-2-(trifluoromethyl)pyridine (1.8 g, 10 mmol) with butyllithium (30 mmol) in the presence of LIDMAE (30 mmol) at −75 °C in hexanes (50 mL), carboxylation, neutralization and crystallization from cyclohexane.

3.4.3. 5-Chloro-2-(trifluoromethyl)pyridine-3-carboxylic acid (8). A similar reaction as above (see preparation of 6-chloro-4-(trifluoromethyl)pyridine-3-carboxylic acid; subsection 3.3.2) performed with 3-bromo-5-chloro-2-(trifluoromethyl)pyridine (5.2 g, 20 mmol) afforded after crystallization from a 6:1 (v/v) mixture of heptane and ethyl acetate colorless needles; mp 137–139 °C; yield: 3.81 g (84%). ^{1}H NMR*: δ=8.88 (d, J=2.2 Hz, 1H), 8.37 (dq, J=2.2, 0.6 Hz, 1H). ^{13}C NMR*: δ=166.3, 150.6, 143.6 (q, J=35 Hz), 138.8, 135.8, 130.6, 122.1 (q, J=275 Hz). Anal. Calcd for $C_7H_3ClF_3NO_2$ (225.55): C 37.27, H 1.34. Found: C 37.15, H 1.41.

3.5. Chlorine/bromine displacement

3.5.1. 2-Bromo-4-(trifluoromethylpyridine-3-carboxylic acid. 2-Chloro-4-(trifluoromethyl)pyridine-3-carboxylic acid (11 g, 50 mmol) and bromotrimethylsilane (20 mL, 23 g, 0.15 mol) were heated slowly (over 2 h) to 100 °C and kept for 4 h at this temperature, while 70 °C warm water was circulated through the spiral of the reflux condenser. Hydrogen chloride and small amounts of chlorotrimethylsilane were allowed to escape through a drying tube filled with calcium chloride. The mixture was then poured into a 2.0 M aqueous solution (0.15 L) of sodium hydroxide. The aqueous phase was washed with diethyl ether (3×0.10 L) before being acidified with hydrochloric acid to pH 1 and extracted with diethyl ether (3×0.10 L). The combined organic layers were dried and evaporated. The residue was recrystallised from a 1:1 (v/v) mixture of ethyl acetate and hexanes; colorless prisms; mp 159–161 °C; 10.8 g (80%). ^{1}H NMR: δ=8.61 (d, J=5.1 Hz, 1H), 7.57 (d, J=5.1 Hz, 1H). ^{13}C NMR: δ=166.0, 1150.7, 139.8, 136.8 (q, J=34 Hz), 131.1, 121.4 (q, J=275 Hz), 119.0 (q, J=4 Hz). Anal. Calcd for $C_7H_3BrF_3NO_2$ (270.00): C 31.14, H 1.12. Found: C 31.09, H 1.12.

3.5.2. 2-Bromo-5-(trifluoromethyl)pyridine-4-carboxylic acid. Analogously from 2-chloro-5-(trifluoromethyl)pyridine-4-carboxylic acid (11 g, 50 mmol); colorless prisms (from ethyl acetate); mp 190–191 °C (decomp.); 11.4 g (84%); ^{1}H NMR: δ=8.88 (s, 1H), 8.08 (s, 1H); ^{13}C NMR: δ=164.8, 149.5 (q, J=6 Hz), 147.4, 142.5, 128.7, 123.9 (q, J=273 Hz), 123.1 (q, J=33 Hz); $C_7H_3BrF_3NO_2$ (270.00): C 31.14, H 1.12. Found: C 31.18, H 1.36.

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