

Halogen Shuffling in Pyridines : Site Selective Electrophilic Substitutions of 2-Chloro-6-(trifluoromethyl)pyridine

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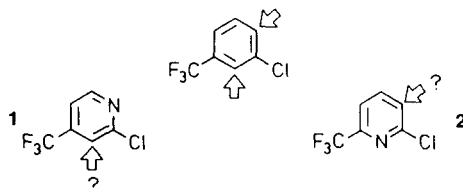
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Abstract : When treated with lithium diisopropylamide in tetrahydrofuran at -85 °C and subsequently with iodine, 2-chloro-6-(trifluoromethyl)pyridine is neatly converted into its 3-iodo derivative. The latter can be quantitatively isomerized to afford 2-chloro-4-iodo-6-(trifluoromethyl)pyridine. Either iodo compound can serve as the starting material for further manipulation in reaction sequences consisting of halogen/metal exchange and electrophilic trapping. © 1998 Elsevier Science Ltd. All rights reserved.

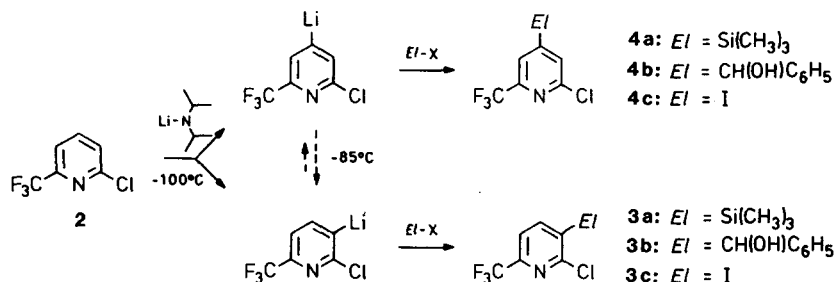
When allowed to react with butyllithium in tetrahydrofuran at -75 °C, 3-chlorobenzotrifluoride undergoes a hydrogen/metal exchange at the angular 2-position, flanked by the two electronegative substituents ¹. Lithiation occurs however at the less acidic 4-position when *sec*-butyllithium is employed as the metal-transferring reagent ¹. Naively one may argue that no proton can be removed from a site where a methine entity has been replaced by an imino-functional nitrogen atom. Therefore, one might predict the two aza-analogous 3-chlorobenzotrifluorides, 2-chloro-4-(trifluoromethyl)pyridine (1) and 2-chloro-6-(trifluoromethyl)pyridine (2) to present no regioselective ambiguities. The present communication deals exclusively with the second substrate. As we shall see, the reality is not as simple as expected.



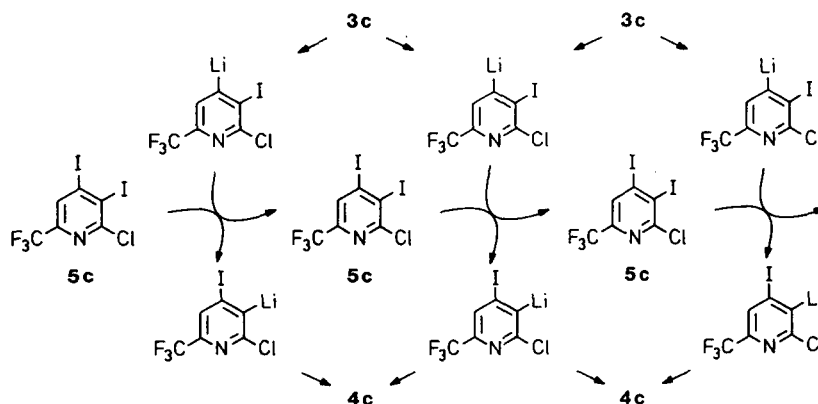
First of all, suitable reaction conditions had to be found which promote the metalation of the tetrahalo- α -picoline and avoid the nucleophilic addition. This can be achieved with 2-chloropyridine only when an elaborate protocol is followed ². In addition, trifluoromethyl groups may complicate things since they have been reported to facilitate nucleophilic addition onto the pyridine ring unless at least one of such moieties is located at the 3-position while the neighboring 2-position is unsubstituted, thus being available for deprotonation ³.

As we soon realized, the reaction temperature is critical. Since at -75 °C extensive decomposition took place, 2-chloro-6-(trifluoromethyl)pyridine (2) was added to a solution of lithium diisopropylamide in tetrahydrofuran at -100 °C. Under these circumstances, protons were simultaneously abstracted from the 3- and

4-position, as previously observed with 2,4-dichloropyridine ⁴ and 2,6-dichloropyridine ⁵ as the substrate. After interception of the organometallic intermediates with typical electrophiles (*e.g.*, chlorotrimethylsilane or benzaldehyde), the regioisomers **3** and **4** were isolated in approximately equal amounts. The 4-position being the most acidic one in unsubstituted pyridine ⁶, it can evidently compensate its remoteness of the chlorine substituent and successfully compete with the 3-position under the conditions of irreversible deprotonation. However, when the temperature was raised to -85 °C, equilibration of the acid-base pairs by reversible reprotonation apparently became effective. The 4-lithio intermediate was totally consumed and converted into the less basic 3-lithio species. The trapping products (**3**) were now regioisomerically homogeneous.



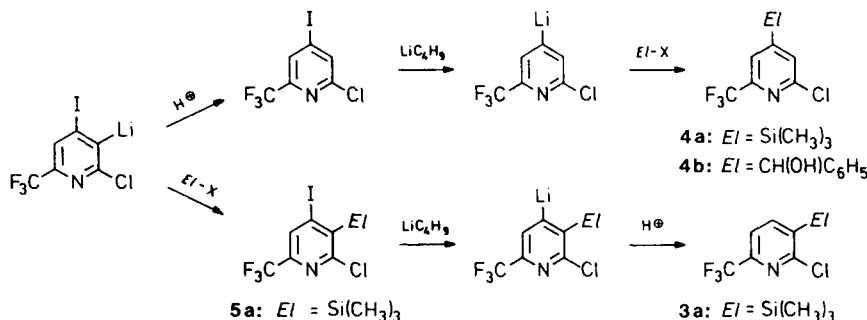
Fortunately, also the 4-substituted isomers can be obtained pure. When 2-chloro-3-iodo-6-(trifluoromethyl)pyridine (**3c**) is incubated with lithium diisopropylamide (LIDA) in tetrahydrofuran, it forms exclusively 2-chloro-4-iodo-6-trifluoromethyl-3-pyridyllithium. Once again an acidity gradient-driven halogen/metal exchange ^{1, 7, 8} is at the origin of the observed halogen migration. 2-Chloro-3-iodo-6-trifluoromethyl-4-pyridyllithium, generated by LIDA-mediated deprotonation of product **3c**, reacts with 2-chloro-3,4-diiodo-6-(trifluoromethyl)pyridine (**5**; accidentally formed in small amounts by iodine transfer to the 4-lithio species from its precursor **3c**) under permutation of the lithium atom at the organometallic 4-position with the iodine at the 3-position of the diiodo compound **5c**. In this way, the more basic 4-lithio species reemerges as the less basic 3-lithio isomer while the diiodide **5c** resurrects in each exchange step, thus capable of assuming the role of a mechanistic turntable.



In agreement with this scheme, 2-chloro-4-iodo-6-trifluoromethyl-3-pyridyllithium was quantitatively formed when substrate 2 was consecutively treated with lithium diisopropylamide (2.0 molar equiv.) and the

diiodo compound **5c** (1.0 equiv.) at $-80\text{ }^{\circ}\text{C}$. The latter product is readily obtained by lithiation of the monoiodide **4c** followed by reaction with iodine.

After neutralization of the 3-lithio intermediate, 2-chloro-4-iodo-6-(trifluoromethyl)pyridine (**4c**) was isolated in excellent yield. Upon treatment with butyllithium or *tert*-butyllithium, the 2-chloro-6-trifluoromethyl-4-pyridyllithium is generated and readily combines with electrophiles to afford the corresponding products (e.g., **4a** and **4b**). Alternatively, the 4-iodo-3-lithio species may be trapped by an electrophile (e.g., chlorotrimethylsilane) and the resulting derivative **5a** be reduced to a product of type **3**.



PROCEDURES AND PRODUCTS

^1H - and ^{13}C -NMR spectra were recorded at 400 and 101 MHz, the samples having been dissolved in deuteriochloroform. For standard working practice see recent publications (e.g., ref. ⁹) from the same laboratory.

2-Chloro-6-(trifluoromethyl)-3-(trimethylsilyl)pyridine (3a): Diisopropylamine (3.5 mL, 2.5 g, 25 mmol) and 2-chloro-6-(trifluoromethyl)pyridine (**2**; 4.5 g, 25 mmol) were consecutively added to a solution of butyllithium (25 mmol) in hexane (17 mL) and tetrahydrofuran (50 mL) at $-85\text{ }^{\circ}\text{C}$. After 4 h at $-85\text{ }^{\circ}\text{C}$, chlorotrimethylsilane (3.2 mL, 2.7 g, 25 mmol) was added. The mixture was poured into water (50 mL) and extracted with dichloromethane ($3 \times 20\text{ mL}$). The combined organic layers were evaporated and the residue purified by column chromatography on silica gel using a 1 : 9 (v/v) ethyl acetate/hexane mixture as the eluent. Product **3a** was collected as a colorless liquid; bp $44 - 47\text{ }^{\circ}\text{C}/0.3\text{ mm Hg}$; n_D^{20} 1.6405; 85%. - ^1H -NMR: δ 7.95 (1 H, dd, J 7.5, 0.6), 7.57 (1 H, d, J 7.5), 0.42 (9 H, s). - ^{13}C -NMR: δ 158.0 (s), 148.6 (q, J 35.2), 146.3 (s), 139.9 (s), 120.7 (q, J 273.8), 118.4 (s), -1.5 (3 C, s). - Analysis: calc. for $\text{C}_9\text{H}_{11}\text{ClF}_3\text{NSi}$ (253.73) C 42.60, H 4.37; found C 42.60, H 4.24%. - **1-(2-Chloro-6-(trifluoromethyl)-3-pyridyl)-1-phenylmethanol (3b)**: Analogously, using benzaldehyde (2.5 mL, 2.7 g, 25 mmol) as the electrophile; bp $125 - 128\text{ }^{\circ}\text{C}/0.8\text{ mmHg}$; 72%. - ^1H -NMR: δ 8.43 (1 H, d, J 8.0), 7.83 (1 H, d, J 8.0), 7.5 (5 H, m), 6.25 (1 H, s), 2.61 (1 H, s). - ^{13}C -NMR: δ 149.7 (s), 146.9 (q, J 36.7), 141.3 (s), 140.4 (s), 137.9 (s), 128.9 (2 C, s), 128.7 (s), 127.2 (2 C, s), 120.7 (q, J 274.0), 119.6 (s), 72.2 (s). - Analysis: calc. for $\text{C}_{13}\text{H}_9\text{ClF}_3\text{NO}$ (287.67) C 54.28, H 3.15; found C 54.00, H 3.24%. - **2-Chloro-3-iodo-6-(trifluoromethyl)pyridine (3c)**: Analogously, using iodine (6.3 g, 25 mmol) as the electrophile; mp $36 - 38\text{ }^{\circ}\text{C}$; 69%. - ^1H -NMR: δ 8.49 (1 H, d, J 8.2), 7.44 (1 H, d, J 8.2). - ^{13}C -NMR: δ 155.3 (s), 150.3 (s), 147.8 (q, J 36.9), 120.7 (q, J 274.7), 119.7 (s), 99.1 (s). - Analysis: calc. for $\text{C}_6\text{H}_2\text{ClF}_3\text{IN}$ (307.44) C 23.44, H 0.65; found C 23.28, H 1.00%.

2-Chloro-4-iodo-6-(trifluoromethyl)pyridine (4c): Exactly as described above except that the substrate **2** (25 mmol) was exposed to lithium diisopropylamide (50 mmol!) at $-100\text{ }^{\circ}\text{C}$ (2 h) and subsequently iodine (25 mmol) was added in the course of 30 min while the temperature was gradually raised from -100 to $-80\text{ }^{\circ}\text{C}$; mp $93 - 95\text{ }^{\circ}\text{C}$; 92%. - ^1H -NMR: δ 8.09 (1 H, s), 8.08 (1 H, s). - ^{13}C -NMR: δ 152.2 (s), 148.4 (q, J 36.4), 136.1 (s), 128.4 (s), 119.7 (q, J 274.7), 107.5 (s). - Analysis: calc. for $\text{C}_6\text{H}_2\text{ClF}_3\text{IN}$ (307.44) C 23.44, H 0.65; found C 23.39, H 1.12%. - **2-Chloro-6-(trifluoromethyl)-4-(trimethylsilyl)pyridine (4a)**: At $-75\text{ }^{\circ}\text{C}$, pyridine **2** (7.7 g,

25 mmol) and *N,N,N',N'*-tetramethylethylenediamine (3.8 mL, 2.9 g, 25 mmol) were dissolved in a mixture of diethyl ether (25 mL) and hexane (17 mL) containing butyllithium (25 mmol). After 15 min, chlorotrimethylsilane (3.2 mL, 2.7 g, 25 mmol) was added. After evaporation of the solvents, the crude product was absorbed on silica gel (10 mL). Elution with a 1 : 3 (v/v) mixture of dichloromethane and hexane from more silica gel (90 mL) afforded white crystals; mp 30 - 34 °C; 80%. - ¹H-NMR : δ 7.79 (1 H, s), 7.72 (1 H, s), 0.34 (9 H, s). - ¹³C-NMR : δ 157.3 (s), 151.5 (s), 147.2 (q, *J* 34.5), 131.8 (s), 122.7 (s), 120.9 (q, *J* 274.7), -1.9 (3 C, s). - Analysis : calc. for C₉H₁₁ClF₃NSi (253.73) C 42.60, H 4.37; found C 42.86, H 4.16%. - *1-(2-Chloro-6-trifluoromethyl-4-pyridyl)-1-phenylmethanol (4b)* : A solution of tetrabutylammonium fluoride (0.3 g, 1 mmol), 2-chloro-6-trifluoromethyl-4-(trimethylsilyl)pyridine (**4a**; 6.2 g, 25 mmol) and benzaldehyde (2.5 mL, 2.7 g, 25 mmol) in tetrahydrofuran (30 mL) was kept 1 h at 25 °C before 5% hydrochloric acid (40 mL) was added. The mixture was extracted with dichloromethane (3 × 20 mL) and evaporated. After column chromatography on silica gel with dichloromethane as the eluent white crystals was obtained; mp 74 - 76 °C; 26%. - ¹H-NMR : δ 7.77 (1 H, s), 7.71 (1 H, s), 7.5 (5 H, m), 5.93 (1 H, d, *J* 3.0), 2.58 (1 H, d, *J* 3.0). - ¹³C-NMR : δ 157.5 (s), 152.2 (s), 148.3 (q, *J* 36.9), 141.3 (s), 129.3 (2 C, s), 129.1 (s), 126.9 (2 C, s), 124.6 (s), 120.7 (q, *J* 274.7), 116.8 (s), 74.6 (s). - Analysis : calc. for C₁₃H₉ClF₃NO (287.67) C 54.28, H 3.15; found C 54.24, H 3.23%.

2-Chloro-4-iodo-6-trifluoromethyl-3-(trimethylsilyl)pyridine (5a) : Diisopropylamine (3.5 mL, 2.5 g, 25 mmol), chlorotrimethylsilane (3.2 mL, 2.7 g, 25 mmol) and 2-chloro-4-iodo-6-(trifluoromethyl)pyridine (7.7 g, 25 mmol) were consecutively added to a solution of butyllithium (25 mmol) in hexane (17 mL) and tetrahydrofuran (50 mL) at -75 °C. The volatiles were evaporated and the residue eluted from silica gel with a 1 : 9 (v/v) mixture of ethyl acetate and hexane to give product **5a** as a white powder; mp 62 - 65 °C; 86%. - ¹H-NMR : δ 8.23 (1 H, s), 0.62 (9 H, s). - ¹³C-NMR : δ 156.7 (s), 147.2 (q, *J* 36.1), 144.1 (s), 131.8 (s), 119.7 (q, *J* 273.1), 116.5 (s), 3.0 (3 C, s). - Analysis : calc. for C₉H₁₀ClF₃INSi (379.62) C 28.48, H 2.65; found C 28.57, H 2.98%. - *2-Chloro-3,4-diiodo-6-(trifluoromethyl)pyridine (5c)* : As described above, but using iodine (6.3 g, 25 mmol) as the electrophile; mp 132 - 134 °C; 59%. - ¹H-NMR : δ 7.99 (1 H, s). - ¹³C-NMR : δ 155.3 (s), 146.9 (q, *J* 36.1), 129.4 (s), 123.7 (s), 119.9 (q, *J* 274.7), 115.0 (s). - Analysis : calc. for C₆HClF₃I₂N (434.34) C 16.63, H 0.23; found C 17.11, H 0.24%.

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