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Regioselective *ortho*-Lithiation of Chloro and Bromo Substituted Fluoroarenes

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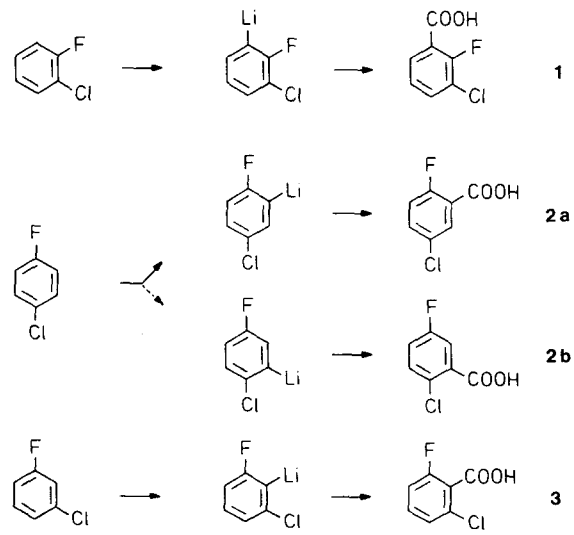
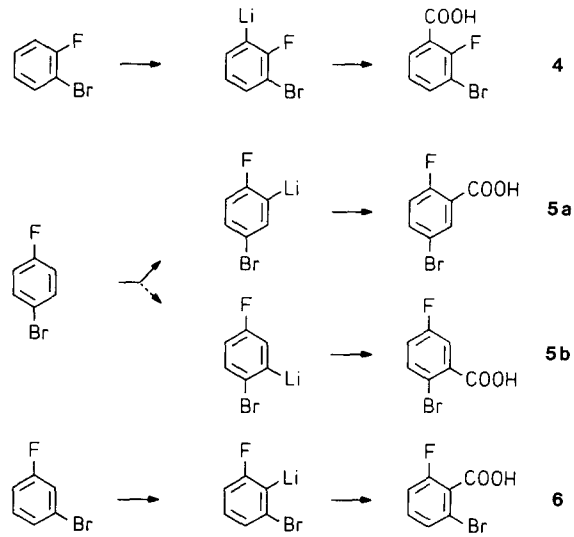
Abstract : Deprotonation of fluoroarenes carrying chlorine or bromine as additional substituents occurs always at a fluorine adjacent position if accomplished with potassium *tert*-butoxide activated butyllithium or lithium 2,2,6,6-tetramethylpiperidide.

When treated with the superbasic mixture [1, 2] of butyllithium and potassium *tert*-butoxide ("LIC-KOR"), fluorobenzene undergoes a smooth *ortho* metalation to afford, after reaction with dry-ice, 2-fluorobenzoic acid in virtually quantitative yield [3]. A second electronegative substituent such as another fluorine atom or a trifluoromethyl group were found to accelerate the deprotonation considerably [3 - 7]. We wondered what the effect of a chloro or bromo substituent on the site and rate of the hydrogen/metal exchange in fluoroarenes would be.

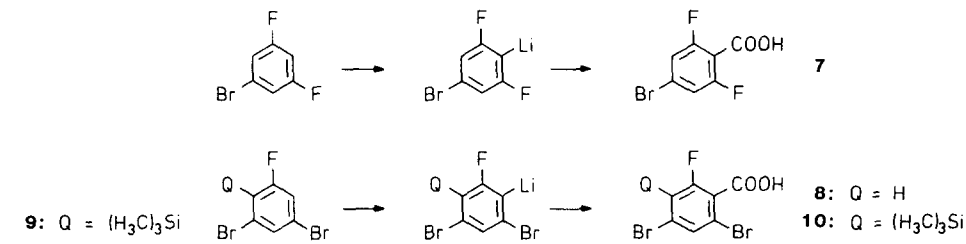
The butyllithium mediated lithiation of *o*-chlorofluorobenzene has already been reported to affect exclusively the fluorine adjacent position producing 3-chloro-2-fluorobenzoic acid (**1**, 70%) upon carboxylation [8], while proton abstraction from the *p*-isomer with lithium diisopropylamide (LIDA) followed by carboxylation afforded 5-chloro-2-fluorobenzoic acid (**2a**, 57%) besides a small amount of the 2-chloro-5-fluoro regioisomer (**2b**, 1%) as a by-product [9]. With the LIC-KOR superbase as the reagent, not only the yields are increased (93% of **1**, 86% of **2a**), but also a perfect regioselectivity is assured. The *m*-isomer is acidic enough to react smoothly with ordinary butyllithium to give 2-chloro-6-fluorobenzoic acid [10, 11] (**3**, 93%) after carboxylation.



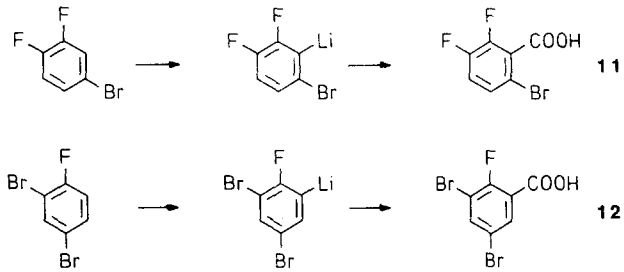
When bromoarenes become the substrates, alkyllithium reagents have to be avoided since they would promote a *halogen*/metal rather than a *hydrogen*/metal exchange. Lithium diisopropylamide (LIDA) in tetrahydrofuran at -75 °C has already been successfully employed for the deprotonation of bromofluorobenzenes [9]. Upon subsequent reaction with dry ice, 3-bromo-2-fluorobenzoic acid (**4**, 73%) was obtained from the *ortho* isomer [8] and 5-bromo-2-fluorobenzoic acid (**5a**, 72%) together with traces of 2-bromo-5-fluorobenzoic acid (**5b**, 0.4%) from the *para* isomer [9]. Replacement of LIDA by lithium 2,2,6,6-tetramethylpiperidide [12] (LITMP) improves both yields (97% of **4**, 82% of **5a**) and selectivity (no trace of **5b**). Analogously, the *meta* isomer gives 2-bromo-6-fluorobenzoic acid (**6**, 79%; or remarkable 93% when a 9 : 1 mixture of LITMP and LIDA is employed).



Quite obviously, fluorine activates ("acidifies") neighboring CH bonds more strongly than any other halogen does. This principle governs also the outcome of LITMP-induced deprotonation/carboxylation sequences having dibromofluoroarenes and bromodifluoroarenes as substrates. Therefore, it is by no means amazing that a CH bond is more readily deprotonated when flanked by two fluorine atoms rather than by one fluorine and one bromine atom let alone by two bromine atoms : 1-bromo-3,5-difluorobenzene affords 4-bromo-2,6-difluorobenzoic acid (**7**, 84%), 1,3-dibromo-5-fluorobenzene affords 2,4-dibromo-6-fluorobenzoic acid (**8**, 81%) and (2,4-dibromo-6-fluorophenyl)trimethylsilane (**9**, prepared in 80% yield by consecutive treatment of 1,3-dibromo-5-fluorobenzene with LITMP and chlorotrimethylsilane) affords 4,6-dibromo-2-fluoro-3-(trimethylsilyl)benzoic acid (**10**, 70%).



Nevertheless, bromine atoms do enhance the proton mobility at neighboring centers. Both, 2-bromo-1,4-difluorobenzene and 1-bromo-2,4-difluorobenzene undergo lithiation exclusively at the position having two adjacent halogen substituents, thus being ultimately converted into 2-bromo-3,6-difluorobenzoic acid [13, 14] and 6-bromo-2,3-difluorobenzoic acid [14] (**11**, 84%), respectively. However, even a single fluorine atom outperforms two cooperating bromine atoms as evidenced by an unprecedented competition experiment : upon consecutive treatment with LITMP and carbon dioxide, 2,4-dibromo-1-fluorobenzene gives 3,5-di-bromo-2-fluorobenzoic acid (**12**, 82%) and no trace of 2,6-dibromo-3-fluorobenzoic acid.



Working Procedures

LIC-KOR as the Metalating Agent : At -75 °C, precooled tetrahydrofuran (50 mL) and potassium *tert*-butoxide (2.8 g, 25 mmol) were added to butyllithium (25 mmol) from which the commercial solvent (hexane) had been stripped off. The fluoroarene was introduced dropwise and under stirring in the course of 5 min. The mixture was kept 40 min at -75 °C before being poured on freshly crushed dry ice. After evaporation of the solvent, the residue was dissolved in water (50 mL), washed with diethyl ether (2 × 20 mL), acidified (to pH 1) and extracted with dichloromethane (3 × 20 mL). Crystallization from hexane or toluene gave a colorless product. - *3-Chloro-2-fluorobenzoic acid* [8] (**1**) : mp 174 - 176 °C; 93%. - ^{1}H-NMR : δ 8.08 (1 H, ddd, *J* 8.1, 6.5, 1.8), 7.80 (1 H, ddd, *J* 8.2, 6.7, 1.7), 7.33 (1 H, td, *J* 8.1, 1.3). - Analysis : calc. for $C_7H_4ClFO_2$ (174.56) : C 48.17, H 2.31; found C 48.24, H 2.10%. - *5-Chloro-2-fluorobenzoic acid* (**2a**) [10]: mp 148 - 149 °C, 86%. - ^{1}H-NMR : δ 8.15 (1 H, dd, *J* 6.3, 2.7), 7.68 (1 H, ddd, *J* 9.1, 4.1, 2.7), 7.28 (1 H, dd, *J* 10.2, 9.1). - Analysis : calc. for $C_7H_4ClFO_2$ (174.56) : C 48.17, H 2.31; found C 48.34, H 2.43%. - *2-Chloro-6-fluorobenzoic acid* (**3**) [15] mp 159 - 161 °C; 93%.

LITMP as the Metalating Agent : At -75 °C, 2,2,6,6-tetramethylpiperidine (4.2 mL, 3.5 g, 12 mmol) and the fluoroarene are consecutively added to a solution of butyllithium (25 mmol) in hexane (17 mL) and tetrahydrofuran (50 mL). The mixture was allowed to stand 2 h at -75 °C before being poured on an excess of freshly crushed dry ice. The products were isolated as described above. - *3-Bromo-2-fluorobenzoic acid* (**4**) [8] : mp 164 - 166 °C; 97%. - ^{1}H-NMR : δ 8.13 (1 H, ddd, *J* 8.4, 6.7, 1.8), 7.95 (1 H, ddd, *J* 8.0, 6.3, 1.7), 7.28 (1 H, td, *J* 8.2, 0.9). - Analysis : calc. for $C_7H_4BrFO_2$ (219.02) C 38.39, H 1.84; found C 38.45, H 1.76%. - *5-Bromo-2-fluorobenzoic acid* (**5a**) [9] : mp 145 - 147 °C; 93%. - ^{1}H-NMR : δ 8.31 (1 H, dd, *J* 6.5, 2.8), 7.83 (1 H, ddd, *J* 9.0, 4.3, 2.7), 7.22 (1 H, dd, *J* 10.3, 9.0) - Analysis : calc. for $C_7H_4BrFO_2$ (219.02) C 38.39, H 1.84; found C 38.40, H 1.95%. - *2-Bromo-6-fluorobenzoic acid* (**6**) [16] : mp 152 - 154 °C; 93%. - ^{1}H-NMR : δ 7.57 (1 H, d, *J* 8.1), 7.42 (1 H, td, *J* 8.3, 5.8), 7.26 (1 H, t, *J* 8.8). - Analysis : calc. for $C_7H_4BrFO_2$ (219.02) C 38.39, H 1.84; found C 38.37, H 1.95%. - *4-Bromo-2,6-difluorobenzoic acid* (**7**) : mp 195 - 197 °C; 81%. - ^{1}H-NMR : δ 7.28 (1 H, d, *J* 7.4). - ^{13}C-NMR : δ 163.1 (s), 160.8 (dd, *J* 260.2, 7.1), 125.3 (t, *J* 12.4), 126.1 (d, *J* 28.2), 110.7 (s). - Analysis : calc. for $C_7H_3BrF_2O_2$ (237.01) C 35.47, H 1.28; found C 35.75, H 1.06%. - *2,4-Dibromo-6-fluorobenzoic acid* (**8**) : mp 136 - 138 °C; 83%. - ^{1}H-NMR : δ 7.77 (1 H, t, *J* 1.5), 7.46 (1 H, dd, *J* 8.7, 1.8). - ^{13}C-NMR : δ 167.4 (s), 159.6 (d, *J* 260.2), 131.8 (d, *J* 3.2), 125.3 (d, *J* 10.5), 122.4 (d, *J* 19.2), 121.3 (d, *J* 4.0), 119.0 (d, *J* 25.0). - Analysis : calc. for $C_7H_3Br_2FO_2$ (297.92) C 28.22, H 1.02; found C 28.29, H 1.12%. - *4,6-Dibromo-2-fluoro-3-(trimethylsilyl)benzoic acid* (**10**) : mp 141 - 145 °C; 70%. - ^{1}H-NMR : δ 7.79 (1 H, d, *J* 1.2), 0.47 (9 H, d, *J* 2.5). - ^{13}C-NMR : δ 169.1 (s), 163.1 (d, *J* 253.8), 133.0 (d, *J* 2.4), 132.2 (d, *J* 13.6), 127.7 (d, *J* 32.9), 122.7 (d, *J* 26.5), 121.4 (d, *J* 5.6), 1.1 (d, *J* 4.8). - Analysis : calc. for $C_{10}H_{11}Br_2FO_2Si$ (370.10) C 32.45, H 3.00; found C 32.63, H 2.76%. - *6-Bromo-2,3-difluorobenzoic acid* (**11**) : mp 114 - 116 °C; 84%. - ^{1}H-NMR : δ 7.53 (1 H, ddd, *J* 9.1, 4.1, 1.8), 7.32 (1 H, td, *J* 9.4, 8.3). - ^{13}C-NMR : δ 167.1 (s), 149.8 (dd, *J* 251.7, 13.3), 148.5 (dd, *J* 259.0, 14.9), 129.0 (s), 124.9 (d, *J* 15.3), 120.1

(d, *J* 17.7), 114.2 (s). - Analysis : calc. for $C_7H_3BrF_2O_2$ (237.01) C 35.47, H 1.28; found C 35.62, H 1.30%.- *3,5-Dibromo-2-fluorobenzoic acid* (**12**) : mp 193 - 195 °C; 82%. - ^{1}H-NMR : δ 8.18 (1 H, dd, *J* 5.9, 2.6), 7.99 (1 H, dd, *J* 5.5, 2.4). - ^{13}C-NMR : δ 164.4 (d, *J* 3.2), 157.7 (d, *J* 261.0), 139.6 (s), 134.2 (s), 122.0 (d, *J* 12.9), 116.5 (d, *J* 4.8), 111.8 (d, *J* 24.0). - Analysis : calc. for $C_7H_3Br_2FO_2$ (297.92) C 28.22, H 1.02; found C 28.33, H 1.03%.

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