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Reagent-Modulated Optional Site Selectivities : The Metalation of *o*-, *m*- and *p*-Halobenzotrifluorides

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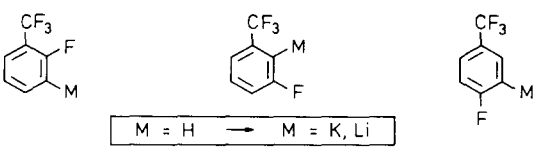
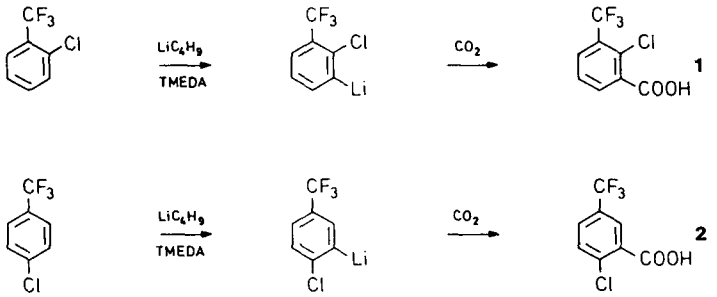
Abstract : Chloro(trifluoromethyl)benzenes and bromo(trifluoromethyl)benzenes undergo deprotonation at a position adjacent to the single halogen substituent when treated with alkyllithiums (at -75 °C) and, respectively, lithium 2,2,6,6-tetramethylpiperidide (at -100 °C) in tetrahydrofuran. Positional ambiguities, if existing, can be exploited to establish optional site selectivities. Thus, butyllithium reacts with 1-chloro-3-(trifluoromethyl)benzene under hydrogen/metal interconversion at the 2-position whereas *sec*-butyllithium attacks exclusively the 6-position. The latter mode of regioselectivity is also exhibited by 1-bromo-3-(trifluoromethyl)benzene in the presence of lithium 2,2,6,6-tetramethylpiperidide, only 2-bromo-4-(trifluoromethyl)phenyllithium being produced. 2-Bromo-6-(trifluoromethyl)phenyllithium is directly inaccessible, but is formed when 2-bromo-3-(trifluoromethyl)phenyllithium, generated at -100 °C, is allowed to isomerize at -75 °C.

Fluorine atoms and trifluoromethyl groups belong to the weakest among all neighboring groups known to promote *ortho*-metalation of hetero-substituted arenes [1]. As we have demonstrated previously [2], the single halogen atom exerts a superior effect compared with the trifluoromethyl moiety since the superbasic mixture of butyllithium and potassium *tert*-butoxide converts 2-, 3- and 4-fluorobenzotrifluoride [1-fluoro-2-, -3- and -4-(trifluoromethyl)benzene] into 2-fluoro-3-(trifluoromethyl)phenyllithium, 2-fluoro-6-(trifluoromethyl)phenyllithium and 2-fluoro-5-(trifluoromethyl)phenyllithium, respectively. We wondered how the corresponding chloro- and bromo(trifluoromethyl)benzenes would behave toward strong bases.

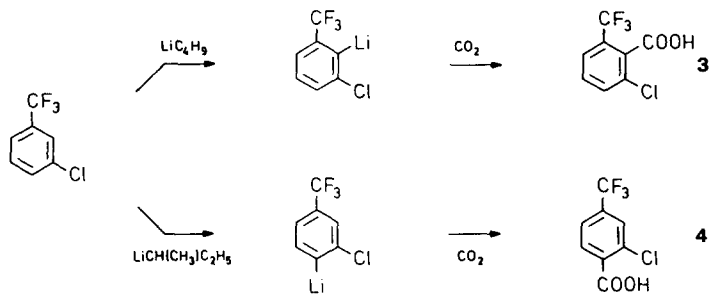


2- and 4-Chlorobenzotrifluoride [1-chloro-2-(trifluoromethyl)benzene and 1-chloro-4-(trifluoromethyl)-benzene] were found to react smoothly with *N,N,N',N'*-tetramethylethylenediamine (TMEDA) activated butyllithium in tetrahydrofuran at -75 °C. The intermediates were trapped after 2 h with dry ice to afford 2-chloro-3-(trifluoromethyl)benzoic acid (**1**; 76%) and 2-chloro-5-(trifluoromethyl)benzoic acid (**2**; 67%). Apparently, the trifluoromethyl moiety stabilizes the aryllithium species towards decomposition by lithium halide elimination

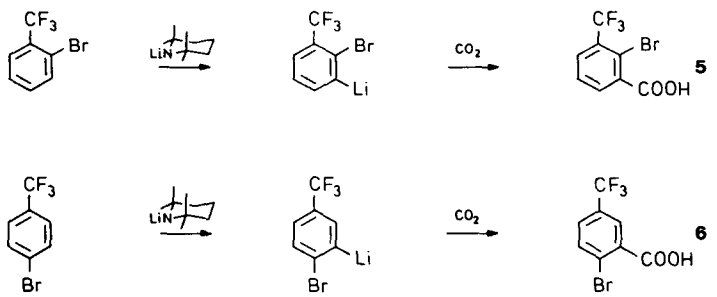
since the metalation of chlorobenzene and simple analogues thereof can only be accomplished at temperatures around -105 °C [3].



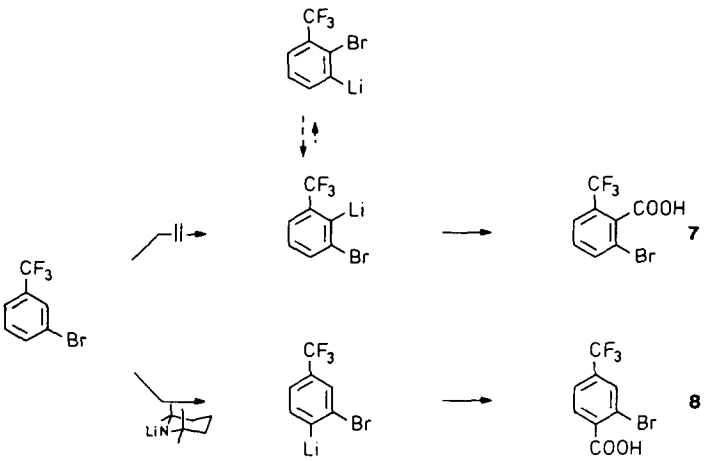
3-Chlorobenzotrifluoride [1-chloro-3-(trifluoromethyl)benzene] is reactive enough to undergo a hydrogen/-metal exchange at the 2-position already with uncomplexed butyllithium. Subsequent carboxylation gave 2-chloro-6-(trifluoromethyl)benzoic acid (**3**; 80%). However, 2-chloro-4-(trifluoromethyl)benzoic acid (**4**; 67%) was isolated as the exclusive reaction product when the same haloarene was consecutively treated with *sec*-butyllithium and dry ice. This is another striking example of optional site selectivity [4]. Obviously, the 2-position is the most acidified and, at the same time, the sterically most hindered one. A subtle tuning of the organo-metallic reagent suffices to make one or the other of these factors dominant and in this way to alter the outcome of the reaction.



A halogen/metal interconversion taking place between bromobenzotrifluorides and alkyllithiums [5], we had to turn to lithium 2,2,6,6-tetramethylpiperidide [6] in order to accomplish the *ortho*-lithiation. 2-Bromobenzotrifluoride [1-bromo-2-(trifluoromethyl)benzene] and 4-bromobenzotrifluoride [1-bromo-4-(trifluoromethyl)-benzene] were indeed deprotonated at -100 °C in tetrahydrofuran and afforded, after carboxylation, 2-bromo-3-(trifluoromethyl)benzoic acid (**5**; 48%) and 2-bromo-5-(trifluoromethyl)benzoic acid (**6**; 85%).



3-Bromobenzotrifluoride [1-bromo-3-(trifluoromethyl)benzene] was only lithiated at the uncongested *ortho*-position, 2-bromo-4-(trifluoromethyl)phenyllithium being the intermediate and 2-bromo-4-(trifluoromethyl)-benzoic acid the carboxylation product (**8**; 85%). The isomeric 2-bromo-6-(trifluoromethyl)benzoic acid (**7**; 71%) could nevertheless be obtained with good yields if 2-bromo-3-(trifluoromethyl)phenyllithium, the intermediate initially generated from 2-bromobenzotrifluoride, was kept 2 h at -75 °C, under which conditions it was completely converted into the less basic and hence thermodynamically more stable 2-bromo-6-(trifluoromethyl)phenyllithium.



A priori two mechanisms can explain how this equilibration is brought about. Lithium bromide may be eliminated and add again [6], though with opposite regiochemistry, to the resulting dehydroarene. Alternatively, trace amounts of 2,3-dibromobenzotrifluoride may act as a turntable for a base catalyzed "halogen dance" as established by many examples in the carbo- and heterocyclic series [7]. The first possibility can be ruled out, since all attempts failed to trap the hypothetical dehydroarene ("aryne") with nucleophiles or dienes. On the other hand, addition of some 2,3-dibromobenzotrifluoride to the reaction mixture was found to accelerate the isomerization.

Working Procedures [8]

2-Chloro-3-(trifluoromethyl)benzoic acid (1) : At -75 °C, butyllithium (25 mmol) in hexane (17 mL) was added to 2-chlorobenzotrifluoride (3.3 mL, 4.5 g, 25 mmol) and TMEDA (3.8 mL, 2.9 g, 25 mmol) in tetrahydrofuran (50 mL). After 1 h at -75 °C, the mixture was poured on freshly crushed dry ice. The solvents were evaporated. The residue was dissolved in water (50 mL), washed with diethyl ether (2 × 20 mL) and acidified with concentrated hydrochloric acid (to pH1). Extraction with dichloromethane (3 × 20 mL) and crystallization from hexane gave a white solid; mp 131 - 133 °C; 76%. - ^{1}H-NMR : δ 8.25 (1 H, dd, *J* 8.0, 1.5), 8.05 (1 H, dd, *J* 8.0, 1.5), 7.64 (1 H, t, *J* 8.0). - ^{13}C-NMR : δ 170.4, 134.8, 132.7, 131.8, 131.1 (q, *J* 5.1), 130.5 (q, *J* 31.3), 126.7, 122.5 (q, *J* 273.9). - Analysis : calc. for $C_8H_4ClF_3O_2$ (224.57) C 42.79, H 1.80; found C 42.78, H 1.89%. - **2-Chloro-5-(trifluoromethyl)benzoic acid (2)** [9]: Analogously from 4-chlorobenzotrifluoride; mp 91- 93 °C; 67%. - ^{1}H-NMR : δ 8.46 (1 H, d, *J* 2.2), 7.89 (1 H, dd, *J* 8.7, 2.2), 7.79 (1 H, d, *J* 8.7). - Analysis : calc. for $C_8H_4ClF_3O_2$ (224.57) C 42.79, H 1.80; found C 43.05, H 2.00%. - **2-Chloro-6-(trifluoromethyl)benzoic acid (3)** : From 3-chlorobenzotrifluoride using butyllithium without adding TMEDA (3 h at -75 °C); mp 124 - 126 °C; 80%. - ^{1}H-NMR : δ 7.68 (1 H, d, *J* 8.0), 7.66 (1 H, d, *J* 7.5), 7.54 (1 H, t, *J*

8.0). - $C_8H_4ClF_3O_2$ (224.57) C 42.79, H 1.80; found C 42.99, H 1.91%. - **2-Chloro-4-(trifluoromethyl)-benzoic acid (4)** : From 3-chlorobenzotrifluoride using *sec*-butyllithium (3 h at -75 °C); mp 114 - 116 °C; 67%. - ^{1}H-NMR : δ 8.13 (1 H, d, *J* 8.2), 7.77 (1 H, d, *J* 1.0), 7.63 (1 H, dd, *J* 8.2, 1.0). - $C_8H_4ClF_3O_2$ (224.57) C 42.79, H 1.80; found C 42.86, H 1.88%.

2-Bromo-3-(trifluoromethyl)benzoic acid (5) : 2,2,6,6-Tetramethylpiperidine (4.2 mL, 3.5 g, 25 mmol) and then dropwise, in the course of 5 min, 2-bromobenzotrifluoride (3.4 mL, 5.6 g, 25 mmol) were added to a solution of butyllithium (25 mmol) in hexane (17 mL) and tetrahydrofuran (50 mL) cooled to -100 °C. After having been kept 2 h at this temperature, the mixture was poured on an excess of freshly crushed dry ice. The solvents were evaporated and the residue dissolved in water (50 mL). The aqueous layer was washed with diethyl ether (2 × 20 mL) and acidified with concentrated hydrochloric acid (to pH 1). Extraction with dichloromethane (3 × 20 mL) and crystallization from hexane afforded a white solid; mp 141 - 143 °C; 18%; 48%, when two equivalents of lithium 2,2,6,6-tetramethylpiperidine were used. - ^{1}H-NMR : δ 8.10 (1 H, dd, *J* 7.8, 1.5), 8.00 (1 H, dd, *J* 8.0, 1.5), 7.67 (1 H, td, *J* 8.0, 0.8). - ^{13}C-NMR : δ 171.1, 135.2, 134.0, 132.1 (q, *J* 31.5), 130.7 (q, *J* 4.8), 127.4, 122.7 (q, *J* 273.7), 119.4. - Analysis : calc. for $C_8H_4BrF_3O_2$ (269.02) C 35.72, H 1.50; found C 35.89, H 1.11%. - **2-Bromo-5-(trifluoromethl)benzoic acid (6)** : Analogously from 4-bromo-benzotrifluoride (but 6 h of metalation at -100 °C); mp 117 - 119 °C; 85%. - ^{1}H-NMR : δ 8.40 (1 H, d, *J* 2.2), 8.01 (1 H, d, *J* 8.5), 7.78 (1 H, dd, *J* 8.5, 2.2). - Analysis : calc. for $C_8H_4BrF_3O_2$ (269.02) C 35.72, H 1.50; found C 36.03, H 0.98%. - **2-Bromo-6-(trifluoromethl)benzoic acid (7)** : From 2-bromobenzotrifluoride which was treated with lithium 2,2,6,6-tetramethylpiperidide, as described above (see the preparation of product **5**), but for 2 h at -75 °C rather than at -100 °C; mp 131 - 133 °C; 71%. - ^{1}H-NMR : δ 7.83 (1 H, d, *J* 8.0), 7.68 (1 H, d, *J* 7.9), 7.45 (1 H, tq, *J* 8.1, 0.8). - Analysis : calc. for $C_8H_4BrF_3O_2$ (269.02) C 35.72, H 1.50; found C 35.86, H 1.15%.- **2-Bromo-4-(trifluoromethl)benzoic acid** [10] **(8)** : From 3-bromobenzo-trifluoride as described above (see the preparation of product **5**); mp 120 - 122 °C; 85%. - ^{1}H-NMR : δ 8.25 (1 H, d, *J* 8.1), 8.12 (1 H, d, *J* 1.0), 7.82 (1 H, dd, *J* 8.4, 1.2). - Analysis : calc. for $C_8H_4BrF_3O_2$ (269.02) C 35.72, H 1.50; found C 35.97, H 1.00%.

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