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Trifluoromethyl-Substituted Phenylsilanes: The Regiochemical Course of Their Metalation Dictated by Buttressing Effects

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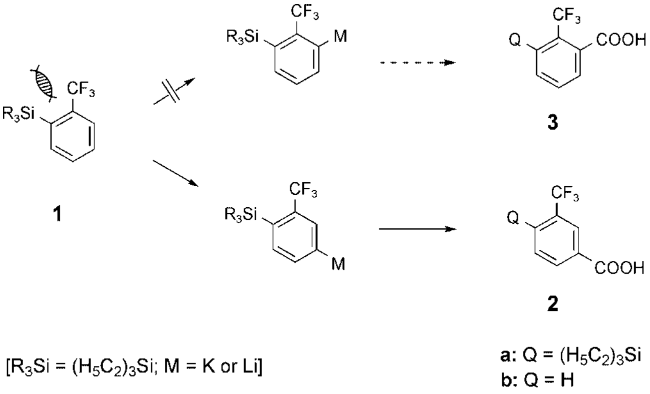
Triethyl[(2-trifluoromethyl)phenyl]silane reacts with the superbasic LIC-KOR mixture of butyllithium and potassium *tert*-butoxide exclusively at the 4-position ("*meta*-metalation") and not at all at the 3-position ("*ortho*-metalation"). Two further substrates which simultaneously contain two trifluoromethyl groups, triethyl[2,4- and 2,5-bis(trifluoromethyl)phenyl]silane, undergo deprotonation at the 5- and 4-position, respectively. Thus, a buttressing effect blocks the attack of metalating agents on the *ortho* position of any trifluoromethyl group which is neighbored, on the other side, by a trialkyl substituent.

Introduction

As previously reported,[1–3] chlorine and bromine atoms are potent transmitters of the steric pressure emanating from an adjacent trialkylsilyl substituent. As we expected trifluoromethyl groups to behave similarly, we have selected three archetypical model compounds belonging to the benzotrifluoride family to verify this hypothesis. The course of the metalation reaction was indeed found to be dominated by buttressing effects in each case.

Results and Discussion

Whereas the superbasic LIC-KOR mixture composed of stoichiometric amounts of butyllithium and potassium *tert*-butoxide metalates benzotrifluoride exclusively at the *ortho* position,[4,5] simple butyllithium in refluxing diethyl ether produces *ortho*, *meta*, and *para* derivatives in a 83:16:1 ratio.[6,7] The proneness to *meta* attack should manifest itself more pronouncedly if a buttressing interaction[1,8,9] discriminates against *ortho*-metalation. In fact, triethyl[(2-trifluoromethyl)phenyl]silane (**1**) was found to undergo hydrogen/metal permutation ("metalation") exclusively at the CF_3-remote 4-position and not at all at the CF_3-adjacent 3-position. After trapping with dry ice, the presence of 4-triethylsilyl-3-(trifluoromethyl)benzoic acid (**2a**; 86%) and the absence of even trace amounts of the isomeric 3-triethylsilyl-2-(trifluoromethyl)benzoic acid (**3a**) was demonstrated by gas chromatographic analysis. To this end, the reaction mixture was first protodesilylated before being treated with an excess of ethereal diazomethane in order to convert the resulting 3-(trifluoromethyl)benzoic acid (**2b**) into its more volatile methyl ester.



1,3-Bis(trifluoromethyl)benzene represents a model case of optional site selectivity. It reacts with *tert*-butyllithium in tetrahydropyran with equal probability at the 4- and the 5-position, with lithium 2,2,6,6-tetramethylpiperidide (LITMP) in tetrahydrofuran solely at the 4-position and with mixed-metal reagents such as LITMP or butyllithium or methyllithium in the presence of potassium *tert*-butoxide solely at the 2-position.[4,5] The latter reaction mode got entirely lost when a triethylsilyl group was introduced next to one of the two trifluoromethyl substituents. Whatever reagent and conditions applied, triethyl[2,4-bis(trifluoromethyl)phenyl]silane (**4**) underwent metalation only at the unbuttressed 5-position to afford, upon silylation and carboxylation, 4,6-bis(trifluoromethyl)-1,3-phenylenebis(triethylsilane) (**5a**; 89%) and 5-(triethylsilyl)-2,4-bis(trifluoromethyl)benzoic acid (**5b**; 91%), respectively. The spectra are

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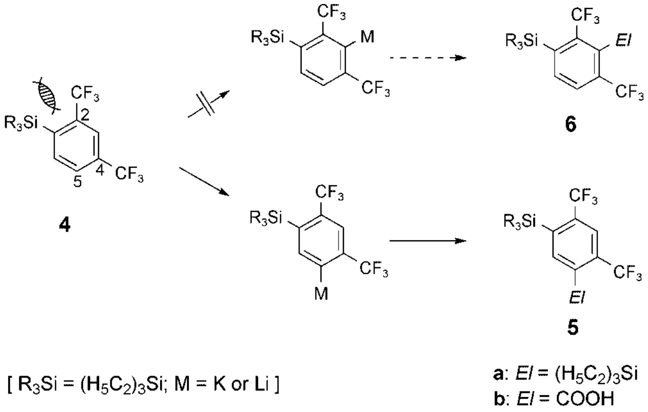
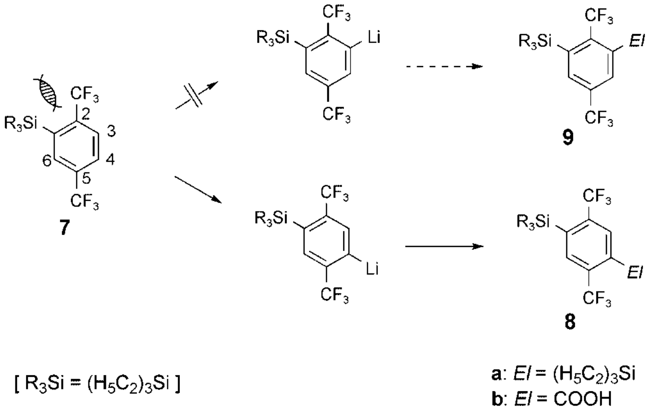
in perfect agreement with the assignment of structure **5a**, characterized by a mirror plane along the C(2),C(5) axis of the bis(silane), and rules out the less symmetrical regioisomer **6a**.



1,4-Bis(trifluoromethyl)benzene has four equivalent vacant positions and hence reacts with standard bases (such as LITMP) smoothly and virtually quantitatively (up to 93% of isolated carboxylation product).[5] The introduction of a triethylsilyl group changed this situation profoundly. The metalation of the silane **7**, accomplished with *sec*-butyllithium, occurred exclusively at the 4-position, the 6-position being sterically inaccessible and the 3-position disabled by a buttressing effect. Depending on the trapping reagent employed, 2,5-bis(trifluoromethyl)-1,4-phenylenebis(triethylsilane) (**8a**; 89%) and 4-triethylsilyl-2,5-bis(trifluoromethyl)benzoic acid (**8b**; 91%) were obtained.



Conclusions

The ordinary kinetic acidity gradient of benzotrifluorides privileging the *ortho* position is suppressed by a vicinal trialkylsilyl substituent. As a consequence, the metalating agent is rerouted to the more remote *meta* position. Although ignored until recently, buttressing effects on deprotonation rates are widespread and need to be taken into account if one wishes to predict the outcome of metalation experiments applied to phenylsilanes carrying halogenated substituents at silyl-adjacent aromatic positions.

Experimental Section

Generalities: For working routine and abbreviations, see related publications from this laboratory.[9–11] Unless specified otherwise, the ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, of samples dissolved in deuteriochloroform.

1. Triethyl[(2-trifluoromethyl)phenyl]silane as the Substrate

Triethyl[(2-trifluoromethyl)phenyl]silane (1): 1-Bromo-2-(trifluoromethyl)benzene (23 g, 0.10 mol) was added to a solution of butyllithium (0.10 mol) in hexane (60 mL) and tetrahydrofuran (0.14 L) cooled in a dry ice/ethanol bath. After 45 min at –75 °C, chlorotriethylsilane (17 mL, 15 g, 0.10 mol) was added to the reaction mixture. Immediate distillation afforded a colorless oil; b.p. 50–52 °C/0.8 Torr; n_D^{20} = 1.4751; d_{20}^{4} = 1.336; yield: 23.4 g (90%). ^{1}H NMR: δ = 7.7 (m, 2 H), 7.51 (symm. m, 2 H), 1.0 (m, 15 H) ppm. ^{13}C NMR: δ = 136.8 (s), 135.4 (q, J = 2 Hz), 135.3 (q, J = 31 Hz), 130.4 (d, J = 1 Hz), 128.8 (s), 126.2 (q, J = 15 Hz), 125.1 (q, J = 273 Hz), 7.4 (s), 3.9 (q, J = 2 Hz) ppm. $C_{13}H_{19}F_3Si$ (260.33): calcd. C 59.97, H 7.36; found C 60.09, H 7.18.

3-Trifluoromethylbenzoic Acid (2b): Potassium *tert*-butoxide (1.7 g, 15 mmol) and the silane **1** (3.9 g, 15 mmol) were consecutively added to a solution of butyllithium (15 mmol) in hexanes (10 mL) and tetrahydrofuran (20 mL) cooled in a dry ice/ethanol bath. After 45 min at –75 °C, the reaction mixture was poured onto freshly crushed dry ice. It was acidified with 2.0 M aqueous hydrochloric acid (10 mL) before being extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried with sodium sulfate. After evaporation of the volatiles, a colorless oil was left behind; yield: 3.92 g (86% with respect to $C_{14}H_{19}F_3O_2Si$). The oil (3.9 g) was treated with tetrabutylammonium fluoride hydrate (19 g, 60 mmol) in refluxing *N*,*N*-dimethylformamide (30 mL) for 60 h. The mixture was poured into water (25 mL) and extracted with diethyl ether (3 × 20 mL). Evaporation of the volatiles gave colorless needles; m.p. 102–103 °C (ref.[6] 103.0–104.5 °C; ref.[12] 106 °C); yield: 1.02 g (36%). According to gas chromatography (30 m, HP-5 methyl siloxane, 150 °C) of the methyl ester obtained after exhaustive exposure of the acid **2b** to ethereal diazomethane, the raw material was uncontaminated by any isomer or other by-product. ^{1}H NMR (400 MHz): δ = 8.1 (m, 2 H), 7.75 (s, broad, 1 H), 7.43 (s, broad, 1 H) ppm.

2. Triethyl[2,4-bis(trifluoromethyl)phenyl]silane as the Substrate

Triethyl[2,4-bis(trifluoromethyl)phenyl]silane (4): 2,2,6,6-Tetramethylpiperidine and 1,3-bis(trifluoromethyl)benzene (15 mL, 21 g, 0.10 mol) were consecutively added to a solution of butyllithium (0.10 mol) in hexanes (60 mL) and tetrahydrofuran (0.14 L), cooled in a dry ice/methanol bath. After 2 h at –75 °C, the mixture was treated with chlorotriethylsilane (17 mL, 15 g, 0.10 mol) stored at +25 °C for 12 h before being distilled under reduced pressure to afford a colorless oil; b.p. 58–60 °C/0.8 Torr; n_D^{20} = 1.4426; d_{20}^{4} = 1.206; yield: 29.5 g (90%). ^{1}H NMR (400 MHz): δ = 7.93 (s, 1 H), 7.82 (s, 1 H), 7.74 (s, 1 H), 0.92 (s, 15 H) ppm. ^{13}C NMR (101 MHz): δ = 141.1 (s), 137.7 (s), 136.6 (q, J = 32 Hz), 131.6 (q, J = 32 Hz), 127.0 (d, J = 3 Hz), 124.8 (q, J = 274 Hz), 123.1 (m, 2 C), 7.2 (s, 3 C) 3.8 (q, J = 3 Hz, 3 C) ppm. $C_{14}H_{18}F_6Si$ (328.37): calcd. C 51.21, H 5.53; found C 51.27, H 5.60.

4,6-Bis(trifluoromethyl)-1,3-phenylenebis(triethylsilane) (5a): 2,2,6,6-Tetramethylpiperidine (4.2 mL, 3.5 g, 25 mmol), potassium *tert*-butoxide (2.8 g, 25 mmol) and the silane **4** (6.8 mL, 8.2 g, 25 mmol) were consecutively added to a solution of butyllithium (25 mmol) in hexanes (15 mL) and tetrahydrofuran (35 mL), cooled in a dry ice/methanol bath. After 2 h at –75 °C, the reaction mixture was treated with chlorotriethylsilane (4.2 mL, 3.8 g, 25 mmol) and distilled immediately; colorless oil; b.p. 148–150 °C/3 Torr; n_D^{20} = 1.4710; d^4_{20} = 1.366; yield: 9.85 g (89%). ^{1}H NMR: δ = 8.04 (s, broad, 1 H), 8.00 (s, broad, 1 H), 0.96 (s, broad, 15 H) ppm. ^{13}C NMR: δ = 145.6 (s), 138.0 (s), 136.2 (q, J = 32 Hz), 124.4 (q, J = 274 Hz), 123.4 (sept, J = 6 Hz), 7.3 (s, 6 C), 3.7 (d, J = 2 Hz, 6 C) ppm. $C_{20}H_{32}F_6Si_2$ (442.64): calcd. C 54.27, H 7.29; found C 54.22, H 6.89.

5-Triethylsilyl-2,4-bis(trifluoromethyl)benzoic Acid (5b): 2,2,6,6-Tetramethylpiperidine (4.2 mL, 3.5 g, 25 mmol), potassium *tert*-butoxide (25 mmol) and the silane **4** (6.8 mL, 8.2 g, 25 mmol) were added consecutively to a solution of butyllithium (25 mmol) in hexanes (15 mL) and tetrahydrofuran (35 mL) cooled in a dry ice/methanol bath. After 2 h at –75 °C, the reaction mixture was poured onto freshly crushed dry ice, neutralized with 2.0 M hydrochloric acid and extracted with ethyl acetate (3 × 25 mL). One tenth of the organic phase was treated with diazomethane until the yellow color persisted. According to gas chromatography (30 m, DB-1, 180 °C, 30 m, DB-WAX, 180 °C; internal calibrated standard: tridecane) the crude product mixture contained 91% of the acid **5b**. The bulk organic phase was concentrated and the residue crystallized from hexanes; colorless needles; m.p. 84–86 °C; yield: 7.63 g (82%). ^{1}H NMR (400 MHz): δ = 8.24 (s, 1 H), 8.08 (s, 1 H), 1.0 (m, 15 H) ppm. ^{13} C NMR (101 MHz): δ = 171.4 (s), 142.3 (s), 139.4 (s), 139.2 (q, J = 33 Hz), 130.8 (s), 130.1 (q, J = 33 Hz), 124.7 (hept, J = 5 Hz), 123.9 (s), 121.2 (s), 7.3 (s, 3 C), 3.6 (q, J = 2 Hz, 3 C) ppm. $C_{15}H_{18}F_6O_2Si$ (372.38): calcd. C 48.38, H 4.87; found C 48.26, H 4.66.

3. Triethyl[2,5-bis(trifluoromethyl)phenyl]silane as the Substrate

Triethyl[2,5-bis(trifluoromethyl)phenyl]silane (7): 1,4-Bis(trifluoromethyl)benzene (21 g, 0.10 mol) was added to a solution of *sec*-butyllithium (0.10 mol) in cyclohexane (70 mL) and tetrahydrofuran (0.13 L) cooled in an dry ice/ethanol bath. After 45 min at –75 °C, the reaction mixture was treated with chlorotriethylsilane (17 mL, 15 g, 0.10 mol) and immediately distilled; colorless oil; b.p. 60–61 °C/0.8 Torr; n_D^{20} = 1.4425; d^4_{20} = 1.211; yield: 30.2 g (90%) ^{1}H NMR: δ = 7.94 (s, broad, 1 H), 7.84 (d, J = 8.1 Hz, 1 H), 7.74 (d, J = 8.0 Hz, 1 H), 0.95 (s, 15 H) ppm. ^{13}C NMR: δ = 138.7 (q, J = 31 Hz), 137.6 (d, J = 2 Hz), 133.3 (q, J = 4 Hz), 132.4 (q, J = 34 Hz), 126.7 (q, J = 6 Hz), 125.8 (q, J = 4 Hz), 124.3 (q, J = 275 Hz), 123.7 (q, J = 273 Hz), 7.2 (s, 3 C), 3.7 (q, J = 3 Hz) ppm. $C_{14}H_{18}F_6Si$ (328.37): calcd. C 51.21, H 5.53; found C 51.33, H 5.51.

2,5-Bis(trifluoromethyl)-1,4-phenylenebis(triethylsilane) (8a): A solution containing the silane **7** (6.8 mL, 8.2 g, 25 mmol) and *sec*-butyllithium (25 mmol) in cyclohexane (20 mL) and tetrahydrofuran (30 mL) was kept at –75 °C for 45 min before chlorotriethylsilane (3.1 mL, 2.7 g, 25 mmol) was added. Upon addition of water (20 mL), extraction with diethyl ether (3 × 25 mL) and evaporation of the volatiles, a residue was collected which crystallized from acetone as colorless needles; m.p. 45–47 °C; yield: 9.85 g (89%). ^{1}H NMR: δ = 7.95 (s, broad, 2 H), 0.94 (s, 30 H) ppm. ^{13}C NMR: δ = 137.2 (s, 2 C), 137.1 (q, J = 31 Hz, 2 C), 134.0 (q, J = 5 Hz, 2 C), 124.7 (q, J = 274 Hz, 2 C), 7.2 (s, broad, 6 C), 3.7 (s, broad, 6 C) ppm. $C_{20}H_{32}F_6Si_2$ (442.64): calcd. C 54.27, H 7.29; found C 54.34, H 6.99.

2,5-Bis(trifluoromethyl)-4-(triethylsilyl)benzoic Acid (8b): The silane **7** (6.8 mL, 8.2 g, 25 mmol) was added to a solution of *sec*-butyllithium (25 mmol) in cyclohexane (19 mL) and tetrahydrofuran (30 mL) cooled in a dry ice/ethanol bath. After 45 min at –75 °C, the reaction mixture was poured onto freshly crushed dry ice before being acidified with 2.0 M hydrochloric acid (10 mL) and extracted with diethyl ether (3 × 25 mL). After drying and evaporation, a yellowish oil was obtained; yield: 8.47 g (91%). ^{1}H NMR: δ = 8.29 (s, broad, 1 H), 8.10 (s, broad, 1 H), 0.96 (s, 15 H) ppm. ^{13}C NMR: δ = 170.9 (s), 142.9 (s), 139.1 (q, J = 32 Hz), 135.1 (q, J = 6 Hz), 130.6 (q, J = 33 Hz), 130.3 (s), 128.7 (q, J = 5 Hz), 123.7 (q, J = 275 Hz), 122.8 (q, J = 275 Hz), 7.2 (s, 3 C), 3.7 (d, J = 2 Hz, 3 C) ppm. $C_{15}H_{18}F_6O_2Si$ (372.38): calcd. C 48.38, H 4.87; found C 48.33, H 4.73.

Acknowledgments

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