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## Lithiation of 2-, 3-, and 4-Fluoroanisole(tricarbonyl)chromium(0) Complexes: a Reversal of Normal Regiocontrol

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Lithiation of tricarbonyl(fluoroanisole)chromium(0) complexes occurs exclusively *ortho* to the fluorine atom, not the oxygen atom as observed in the uncomplexed arenes; the X-ray structure of complex (1) shows that the specificity is not caused by steric inhibition of lithium base co-ordination by oxygen.

Directed lithiation is a widely used and powerful technique for the regiocontrolled synthesis of polyfunctional aromatics.<sup>1</sup> Competition studies have produced<sup>2</sup> a general order of directing ability as:  $CONR_2 > SO_2NR_2 > 2$ -oxazolines >  $CH_2NR_2 > OMe > NMe_2 \approx F$ . Because of its frequent occurrence in natural products and bioactive molecules, the methoxy group is a very commonly used directing function<sup>1</sup> which in simple molecules takes complete precedence over fluorine.<sup>2</sup> We have previously shown that lithiation of tricarbonyl[4-fluoro(tri-isopropylsiloxy)benzene]chro-



Scheme 1. Reagents and conditions: i, Bu<sup>n</sup>Li, tetrahydrofuran (THF), -78 °C, 1 h; ii, PhNCO, -78 °C; iii, ClCO<sub>2</sub>Me, -78 °C; iv, Me<sub>3</sub>SiCl, -78 °C.



Scheme 2. Reagents and conditions: as Scheme 1.

mium(0) occurs exclusively *ortho* to fluorine.<sup>3</sup> We now report that the bulky silyl blocking group is not necessary for this effect. The attachment of the chromium unit alone reversed the normal selectivity.

Tricarbonyl(4-fluoroanisole)chromium(0)  $(1)^{4\dagger}$  was lithiated (BunLi, THF, -78 °C, 1 h) (Scheme 1) and the resulting species quenched at -78 °C with chlorotrimethylsilane to give the complex (3,  $R = SiMe_3$ ) (93%) and with methyl chloroformate to give  $(3, R = CO_2Me)$  (75%). The regiochemistry of lithiation was determined by both spectral and chemical methods. Nuclear Overhauser effect (n.O.e.) difference spectra of the product  $(3, R = SiMe_3)$  showed, on irradiation of the O-methyl group ( $\delta$  3.62), enhancements of two protons at  $\delta$  5.22 (9%, 2-H) and  $\delta$  5.45 (10%, 6-H). Conversely, irradiation of the trimethylsilyl group produced an enhancement of one proton at  $\delta$  5.22 (14%, 2-H). Reaction of the lithiated species with two equivalents of phenyl isocyanate gave the cyclised product (2), (72%) by a process previously described by us.5 These reactions were very clean and no products of lithiation ortho to oxygen were detectable by t.l.c. or in the n.m.r. spectra of the crude reaction mixtures.



Scheme 3. Reagents and conditions: i-iv as Scheme 1; v, MeI, -78 °C.

Lithiation *ortho* to fluorine was thus unambiguously established.

Analogous lithiation of tricarbonyl(2-fluoroanisole)chromium(0) (4) (synthesised in 51% yield using the method in ref. 4) and quenching with chlorotrimethylsilane or methyl chloroformate gave the 3-substituted anisoles (6,  $R = SiMe_3$ or CO<sub>2</sub>Me) in 88% and 77% yields respectively (Scheme 2). Again the regiospecificity of the lithiation was confirmed by reaction of the lithiated intermediate with two equivalents of phenyl isocyanate to give the quinazolinedione complex (5) (89%).

Lithiation of the 3-fluoroanisole complex (7) (synthesised in 40% yield using the method in ref. 4) and quenching with phenyl isocyanate gave the complex (8) (50%) (Scheme 3) as expected. Quenching of the lithio intermediate with chloro-trimethylsilane or iodomethane produced the 2-substituted complexes (9,  $R = SiMe_3$  and Me) in 98% and 94% yields respectively. No other isomers were detectable by t.l.c. or n.m.r. spectroscopy. In neither the 2- or 3-fluoroanisole complexes, (4) or (7), were any isomeric products or products of polylithiation detected.

The compounds (9) were further lithiated and quenched as before. Again, only the products of lithiation *ortho* to fluorine were found. Thus lithiated (9, R = Me), on reaction with phenyl isocyanate, gave quinazolinedione complex (10) (69%) and with chlorotrimethylsilane gave the 1,2,3,4-tetra-substituted benzene complex (11, R = Me,  $R' = SiMe_3$ ) (79%). Lithiated complex (9,  $R = SiMe_3$ ), on reaction with iodomethane or methyl chloroformate, gave the complexes (11,  $R = SiMe_3$ , R' = Me, yield 91%, or CO<sub>2</sub>Me, yield 52%) respectively.

The obvious explanation of the specificity is that the methoxy group is forced to adopt a conformation with the methyl *anti* to the chromium unit and the oxygen is sterically prohibited from co-ordinating the incoming base.<sup>6</sup> However,

 $<sup>\</sup>dagger$  All new compounds were fully characterised by spectroscopy (n.m.r., i.r., m.s.) and microanalysis.



Figure 1. X-Ray crystal structure of (1).

X-ray diffraction analysis of the 4-fluoroanisole complex (1)shows that, at least in the solid state, the methoxy group lies almost in the plane of the arene ring (Figure 1) as it does in the anisole complex itself.<sup>7</sup> The anisole complex is readily lithiated under the above conditions,<sup>8</sup> yet the presence of the fluorine atom in (1) completely diverts the site of lithiation.

In a control experiment, 1 equivalent each of fluorobenzene complex and anisole complex were lithiated with 0.88 equi-

Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1, 1986.

valent of n-butyl lithium and the anions quenched with chlorotrimethylsilane to produce respectively 93% and 3% (based on n-butyl lithium) of *ortho*-silylated products. In these complexes therefore, co-ordination effects must be unimportant and the dominant inductive effect of fluorine is the determinant of kinetic acidity.

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<sup>‡</sup> Crystal Data: C<sub>10</sub>H<sub>7</sub>O<sub>4</sub>FCr, M = 262.2, monoclinic, a = 6.694(2), b = 10.345(3), c = 15.462(3) Å,  $\beta = 91.47(2)^\circ$ , U = 1070 Å<sup>3</sup>, space group  $P2_1$ , Z = 4 (2 independent molecules),  $D_C = 1.63$  g cm<sup>-3</sup>,  $\mu$ (Cu- $K_{\alpha}$ ) = 91 cm<sup>-1</sup>. Data were measured on a Nicolet R3m diffractometer with Cu- $K_{\alpha}$  radiation (graphite monochromator) using  $\omega$ -scans. The structure was solved by direct methods and refined anisotropically to give R = 0.031,  $R_W = 0.034$  for 1510 independent observed reflections [ $|F_0| > 3\sigma(|F_0|)$ ,  $\theta ≤ 58^\circ$ ].