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

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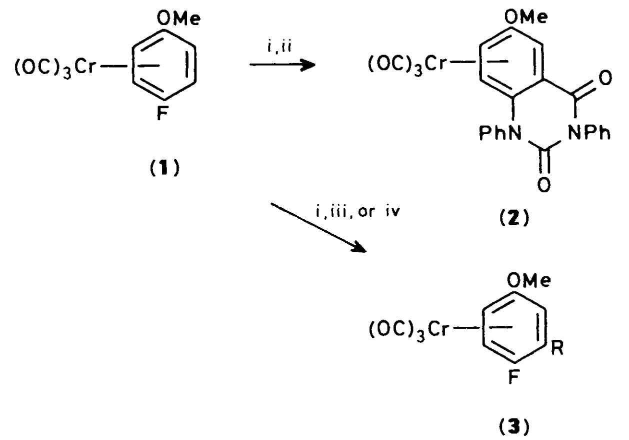
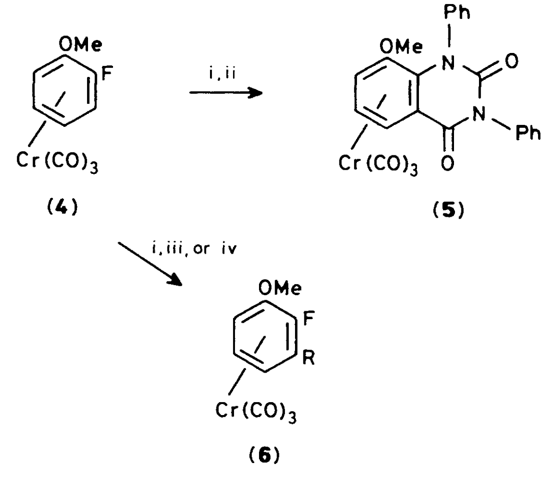
Lithiation of tricarbonyl(fluoroanisole)chromium(0) complexes occurs exclusively *ortho* to the fluorine atom, not the oxygen atom as observed in the uncomplexed arenes; the *X*-ray structure of complex (**1**) shows that the specificity is not caused by steric inhibition of lithium base co-ordination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

Directed lithiation is a widely used and powerful technique for the regiocontrolled synthesis of polyfunctional aromatics.[1] Competition studies have produced[2] 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[1] which in simple molecules takes complete precedence over fluorine.[2] We have previously shown that lithiation of tricarbonyl[4-fluoro(tri-isopropylsiloxy)benzene]chro-



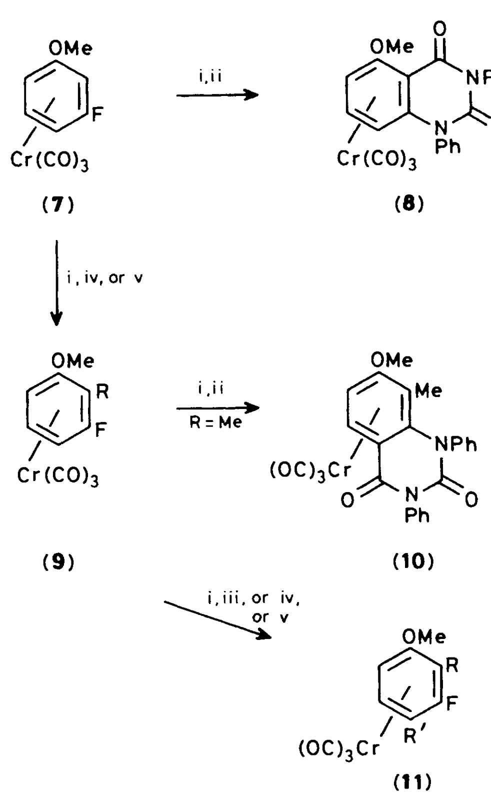
Scheme 1. *Reagents and conditions:* i, Bu^nLi, tetrahydrofuran (THF), −78 °C, 1 h; ii, PhNCO, −78 °C; iii, $ClCO_2Me$, −78 °C; iv, Me_3SiCl, −78 °C.



Scheme 2. *Reagents and conditions:* as Scheme 1.

mium(0) occurs exclusively *ortho* to fluorine.[3] 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]† was lithiated (Bu^nLi, 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 (δ 3.62), enhancements of two protons at δ 5.22 (9%, 2-H) and δ 5.45 (10%, 6-H). Conversely, irradiation of the trimethylsilyl group produced an enhancement of one proton at δ 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_2Me) 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 chlorotrimethylsilane 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-tetrasubstituted 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_2Me, 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.[6] However,

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† All new compounds were fully characterised by spectroscopy (n.m.r., i.r., m.s.) and microanalysis.

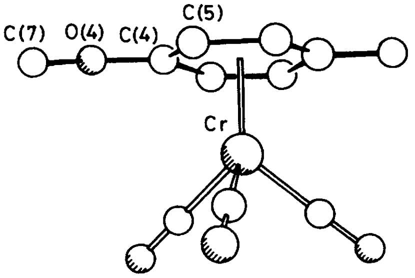

Figure 1. *X*-Ray crystal structure of (**1**).

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.[7] The anisole complex is readily lithiated under the above conditions,[8] 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 equivalent 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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‡ *Crystal Data:* $C_{10}H_7O_4FCr$, $M = 262.2$, monoclinic, $a = 6.694(2)$, $b = 10.345(3)$, $c = 15.462(3)$ Å, $\beta = 91.47(2)°$, $U = 1070$ Å^3, space group $P2_1$, $Z = 4$ (2 independent molecules), $D_C = 1.63$ g cm^{-3}, $\mu(\text{Cu-}K_\alpha) = 91$ cm^{-1}. Data were measured on a Nicolet R3m diffractometer with Cu-K_α radiation (graphite monochromator) using ω-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 $[|F_o| > 3\sigma(|F_o|), \theta \leq 58°]$.

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.