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FLUORINE DIRECTED LITHIATION IN TRICARBONYLARENECHROMIUM(0) COMPLEXES: THE REGIOSPECIFIC SYNTHESIS OF POLYSUBSTITUTED ARENES.

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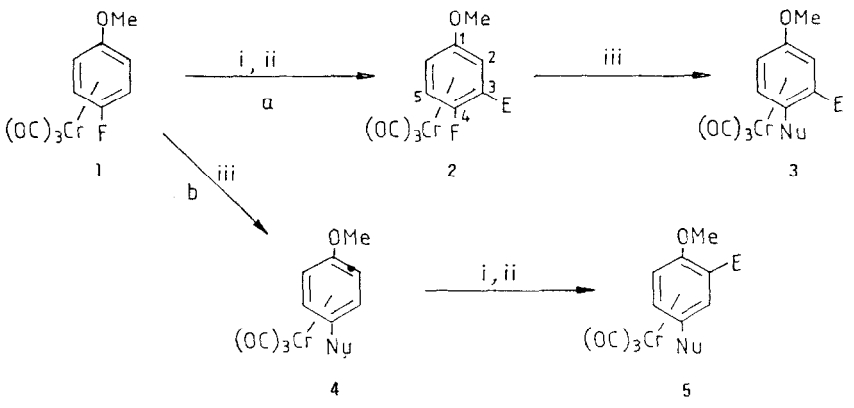
Summary: Lithiation/electrophilic quenching of the isomeric tricarbonylfluoroanisole chromium(0) complexes in combination with nucleophilic displacement of the fluorine by amine and thiolate allows the totally regiocontrolled synthesis of a range of 1,2,3-, 1,2,4-, and 1,2,3,4,5-polysubstituted arenes.

The withdrawal of electron density from an arene ring consequent on complexation with a tricarbonylchromium unit has long been known to enhance the acidities of the arene protons[1] and in the presence of functional group, directed lithiations, adjacent[2] or remote[3], are achieved with ease. Recently we have established that coordination effects in these directed lithiations are less important than inductive effects[4] and thus, in contrast to the uncomplexed series, a fluorine substituent is more powerfully ortho directing than a methoxy group. This property, taken with the ease of displacement of the fluoride ion by a variety of nucleophiles[5], means that a new order of functional group directing abilities can be constructed (see later) and allows the fully regiospecific synthesis of polysubstituted aromatics not readily accessible by conventional means. We now illustrate the power of the method using the isomeric fluoroanisole complexes as the starting units.

Tricarbonyl(4-fluoroanisole)chromium(0)[6] (1) was lithiated with 1 equivalent of n-butyl lithium in THF at -78°C and the lithiated intermediate (2, E = Li) quenched with chlorotrimethylsilane, methyl chloroformate, or methyl iodide to give the corresponding products[7] (2, E = $SiMe_3$, CO_2Me, Me) in 93, 75 and 72% yield respectively (Scheme 1a). In the latter case, because of separation problems, the product was estimated by nmr spectroscopy. A 14% yield of the dimethylated product (2, 3,5-Me_2) was also detected. The products (2) were reacted with pyrrolidine in acetonitrile at room temperature to yield the complexes (3, E = H, CO_2Me, Me; Nu = N-pyrrolidinyl) in 60, 89 and 87% yield respectively. The silyl residue of (2, E = $SiMe_3$) was completely removed by the fluoride ion[8] liberated by the displacement.

Conversely, initial displacement of the fluoride to [4, Nu = N-pyrrolidinyl(81%) or SCH_2Ph (83%)] (Scheme 1b) followed by the lithiation/quench process gave the products [5, Nu = N-pyrrolidinyl, E = Me (92%) or E = CO_2Me (77%)] and [5, Nu = SCH_2Ph, E = CO_2Me (60%)] isomeric with (3). Since the chromium units are readily removed under mild oxidative[9] and/or photochemical conditions[10], these results demonstrate the unique synthetic equivalence for complex (1) expressed in Figure 1 with the added benefit that the nucleophilic sites can be substituted in a totally controlled and sequential manner.



Reagents and Conditions: i, n-BuLi/THF/-78°C; ii, E ($ClSiMe_3$, $ClCO_2Me$, MeI)/THF/-78°C; iii, Nu (Pyrrolidine/MeCN; $NaSCH_2Ph$/THF; $PhCH_2NH_2$), r.t.

Scheme 1

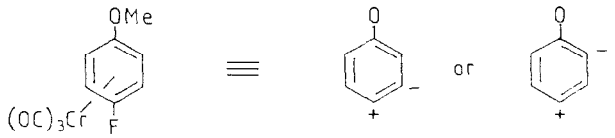
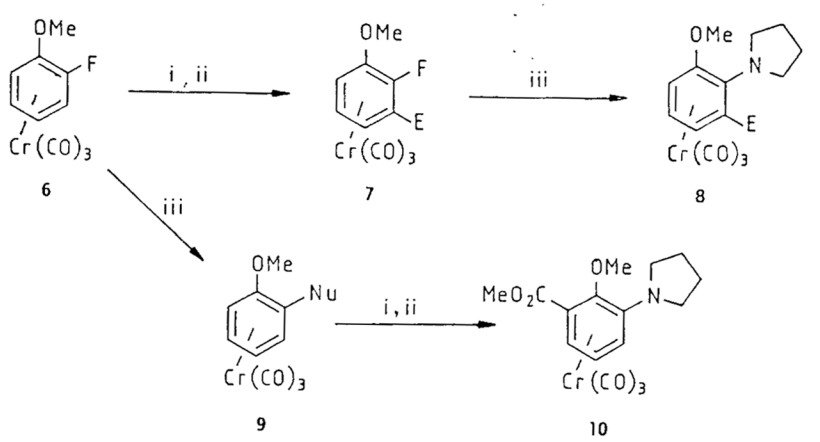


Figure 1

The displacement of F by amine (in acetonitrile) or thiolate (in THF) gives products equivalent to NR_2 and SR having precedence over OR in the initial lithiation step thus effectively reversing the normally observed selectivities[11].

Extension of these reactions to 2-fluoroanisole complex (6)[6] gave a similarly controlled array, now of 1,2,3-trisubstituted benzene complexes (Scheme 2). So prepared were the compounds [7, E = Me (89%) and CO_2Me (77%)], [8, E = CO_2Me (98%)], [9, Nu = N-pyrrolidinyl (86%)], SCH_2Ph (90%)] and (10, 71%). The synthetic equivalence of (6) is thus established as in Figure 2, again with the potential for a controlled sequence of attack at the nucleophilic sites.

The 3-fluoroanisole complex (11) proved to be even more versatile (Scheme 3). In addition to compounds previously reported[4], this sequence gave (12, 98%), [13, E = Me (91%), CO_2Me (52%)], [14, Nu = N-pyrrolidinyl (86%), $NHCH_2Ph$ (80%), SCH_2Ph[12] (78%), F (77%)], (15, 72%) and [16, Nu = N-pyrrolidinyl (90%), F (92%)]. The synthetic equivalence of (11) is given in Figure 3 and inherent in this is the potential for attack at any or all of the nucleophilic sites by an appropriate choice of the sequence.



Reagents and Conditions: as above

Scheme 2

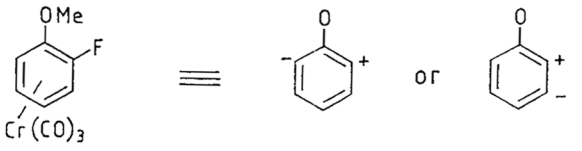
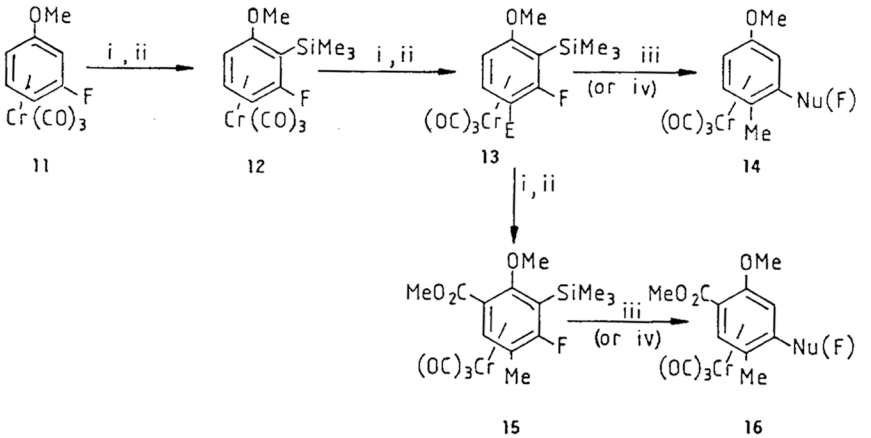


Figure 2



Reagents and Conditions: as above and iv, TBAF/THF/r.t.

Scheme 3

Figure 3

The yields reported above are all those of the pure, isolated product, and with the one exception cited above, the only other compounds detectable by tlc analysis and nmr spectroscopy were the unchanged starting materials. These reactions can clearly be tailored to provide other functional group arrays as desired and represent a very powerful method for the regiospecific synthesis of polyfunctionalised aromatics.

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12. In the thiolate displacemt reaction, only partial desilation occurred and tetrabutylammonium fluoride/THF (1 equ.) was added to complete the process.

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