

Reactions of aryloxy anions with organometallic aryl cation equivalents; a route to substituted diphenyl ethers

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Abstract

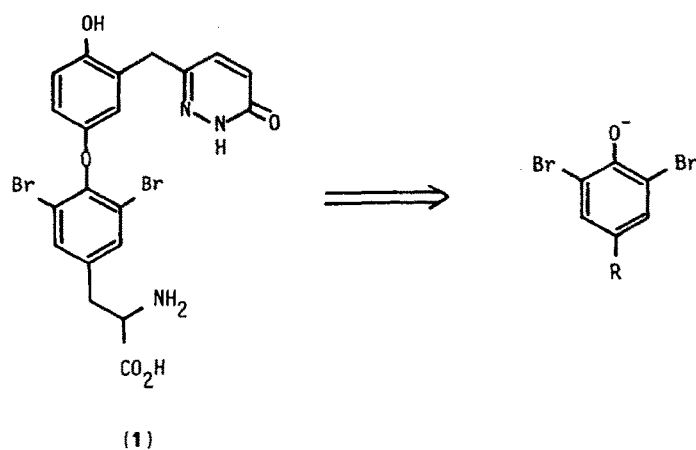
Tricarbonyl(1,4-dichlorobenzene)chromium(0) and chlorobenzene(cyclopentadienyl)iron(II) hexafluorophosphate undergo nucleophilic substitution with sodium phenoxide to give tricarbonyl(4-chloro-1-phenoxybenzene)chromium(0) and phenoxybenzene(cyclopentadienyl)iron(II) hexafluorophosphate, respectively. In the former case, the second chlorine is subsequently displaced by methoxide, and this represents a potentially versatile synthesis of substituted diphenyl ethers. Neither of the complexes react with 2,6-dibromo-4-methylphenoxide, but both phenoxides add to substituted tricarbonylcyclohexadienylmiron complexes to give neutral tricarbonyldieneiron(0) complexes.

Introduction

SK&F L-94901 (1) is a novel, selective, thyromimetic which shows hypocholesterolaemic activity [1]. The key step in any synthesis of this compound or related compounds involves the formation of the hindered diphenyl ether. We have thus been interested in new syntheses of diphenyl ethers and of hindered diphenyl ethers, particularly those based on the disconnection shown in Scheme 1, involving the use of a 2,6-dihalophenoxide as a nucleophilic entity and organometallic complexes as aryl cation equivalents. The need for milder methods for the formation of diphenyl ethers is well recognised [2].

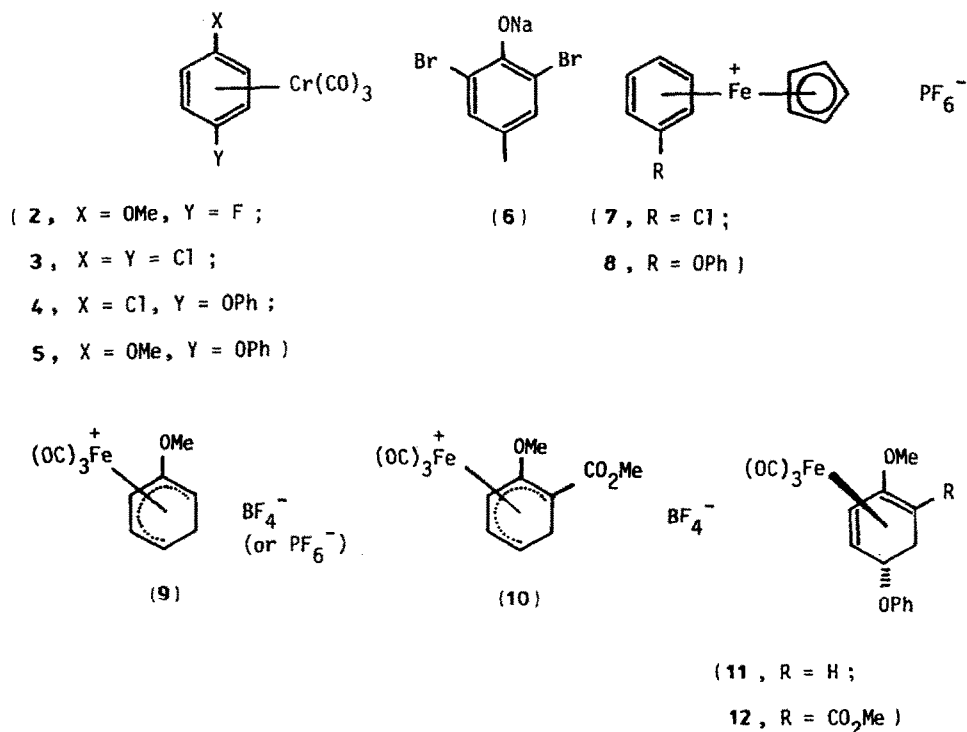
Results and discussion

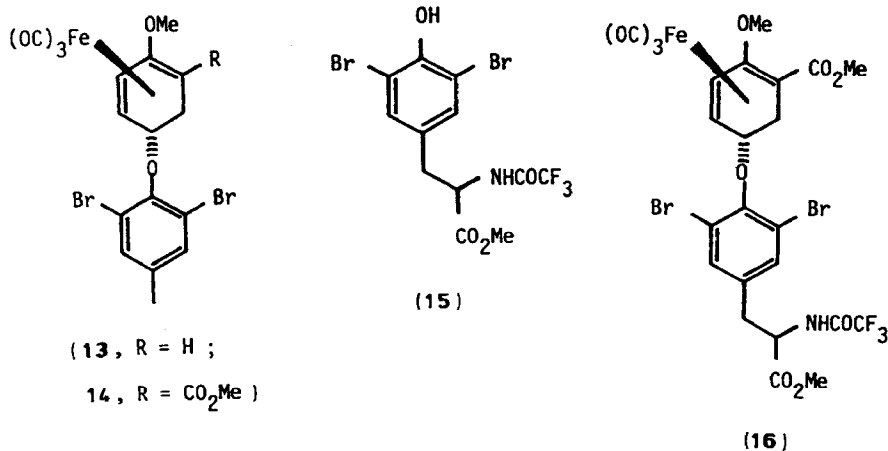
We first examined the nucleophilic substitution of suitably substituted aryl halides activated by the presence of a tricarbonylchromium(0) residue. Treatment of tricarbonyl(4-fluoroanisole)chromium(0) (2) with 5 equivalents of sodium phenoxide in dimethylsulphoxide (DMSO) at temperatures of up to 100 °C gave no product of



Scheme 1

nucleophilic substitution as shown by thin layer chromatography. It was envisaged that the lack of reactivity in this case could be overcome by the use of the 1,4-dichlorobenzene complex 3. Furthermore, on the basis of the above result, some selectivity of the two chlorine atoms towards displacement might be observed that would allow the introduction of two different substituents. (Other examples of this have been reported [3,4,5]). Further elaboration of the complexes produced during this sequence might also be possible [6].





Complex 3 did, indeed, react smoothly with 5 equivalents of sodium phenoxide in DMSO at room temperature to give, after aqueous work-up, the product of monosubstitution 4. This complex was treated, without purification, with 9 equivalents of sodium methoxide in DMSO at room temperature for 2 h to give 5 in 59% overall yield after purification by flash chromatography. Of the solvents examined, only in DMSO did the displacements occur. Removal of the tricarbonylchromium(0) residue can be readily achieved by mild oxidation [7].

This methodology thus represents a mild and potentially versatile route to substituted diphenyl ethers. Unfortunately, the dichlorobenzene complex 3 gave no product of nucleophile substitution on treatment with 5 equivalents of the 2,6-dibromophenoxide 6 in DMSO at temperatures of up to 100°C.

Our attention next turned to the nucleophilic substitution of aryl halides coordinated to the cyclopentadienyliron(II) residue [8,9]. Aryl halides in these complexes are significantly more activated towards nucleophilic substitution [10]. As expected, displacement of chloride from 7 proceeded smoothly on treatment with 1 equivalent of sodium phenoxide in tetrahydrofuran (THF) to afford 8 in a yield of 90%. However, treatment of 7 with 3 equivalents of the dibromophenoxide 6 in THF at temperatures of up to 65°C gave no product of nucleophilic substitution.

These results illustrate the poor nucleophilicity of the 2,6-dibromophenoxide 6 which is caused by both steric and electronic factors. We reasoned that we would be able to overcome this problem by the use of tricarbonylcyclohexadienyliron complexes since these are known to react, regiospecifically, with a range of nucleophiles under mild conditions [11,12], and the formation of sterically crowded centres is well tolerated [13]. Reaction of phenoxide with the non-substituted complex has previously been reported [14,15].

Reaction of the substituted complexes 9 and 10 with 1 equivalent of sodium phenoxide in THF at -65°C gave the neutral diene complexes 11 and 12, respectively, in virtually quantitative yield. We were pleased to find that under the same, and remarkably mild conditions, treatment of 9 and 10 with the dibromophenoxide 6 gave 13 and 14, respectively, and again in virtually quantitative yield.

We have also shown that the addition can be carried out in the presence of a protected amino-acid side chain. The required phenol 15 is prepared from L-tyrosine

and is obtained as a single enantiomer [16]. This was treated with sodium hydride to give the corresponding phenoxide, which was treated with the complex **10** to give the neutral complex **16** in 93% yield. The NMR spectrum of the complex showed two equal and distinct sets of signals for the 6α proton, indicating a 1/1 mixture of diastereoisomers. (We assume that no racemisation of the protected amino-acid occurs during the reaction).

These neutral diene complexes proved to be relatively unstable. Complex **13**, the least stable, decomposes in deuterated chloroform at room temperature. The major pathway for decomposition presumably involves decomplexation and elimination of phenol, although loss of phenoxide to give the cationic complexes **9** and **10** may also take place. Two main methods have been employed in an attempt to convert the diene complexes into diphenyl ethers. First, removal of the metal using trimethylamine-*N*-oxide and subsequent oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) [17], and secondly direct oxidation with palladium on charcoal [18]. Neither of these methods have given diphenyl ethers; the main problem being elimination of the phenol from the uncomplexed diene. These results are perhaps not surprising, especially since this type of dehydrogenation process is not facile.

Experimental

The ^1H NMR spectra were recorded on a Bruker AM 250 or Bruker AM 360 instrument with Me_4Si an internal standard. Mass spectra were recorded on a VG 7070F instrument. IR spectra were recorded on a Perkin-Elmer 298 spectrophotometer. Elemental analyses were obtained with a CEC 240 XA elemental analyser. Melting points were determined in open capillary tubes and are uncorrected. All experiments were conducted under nitrogen. Sodium phenoxide and sodium 2,6-dibromo-4-methylphenoxide (**6**) were prepared by treatment of the corresponding phenol with a suitable base, e.g. sodium methoxide in methanol or sodium hydride in THF, followed by evaporation of solvent. Tricarbonyl(1,4-dichlorobenzene)chromium(0) (**3**) was prepared as previously described [5] and was obtained as a 1/1 mixture of complex and free arene. Tricarbonyl(4-fluoroanisole)chromium(0) (**2**) [19], chlorobenzene(cyclopentadienyl)iron(II) hexafluorophosphate (**7**) [20] and tricarbonyl(2-methoxy-1-methoxycarbonylcyclohexadienylium)iron tetrafluoroborate (**10**) [21,22] have been described previously. Tricarbonyl(2-methoxycyclohexadienylium)iron cation (**9**) was either purchased from Aldrich as its hexafluorophosphate salt or prepared as its tetrafluoroborate salt as previously described [23].

Tricarbonyl(4-methoxy-1-phenoxybenzene)chromium(0) (5)

Sodium phenoxide (100 mg, 0.86 mmol) was added to a stirred solution of tricarbonyl(1,4-dichlorobenzene)chromium(0) (**3**) (45.6 mg, 0.16 mmol) in deoxygenated DMSO (6 ml) under N_2 . The mixture was stirred in the absence of light for 15 h then diluted with ether, washed with water, and dried over sodium sulphate. Removal of solvent gave **4** as a yellow gum. This was dissolved in dry, deoxygenated DMSO (2 ml) and to the solution was added sodium methoxide (83 mg, 1.5 mmol) in dry deoxygenated DMSO (4 ml). The mixture was stirred under N_2 in the absence of light for 2 h, diluted with ether, and washed with 1 *M* HCl then with brine. The aqueous layers were extracted with ether, and the combined ethereal solutions dried over sodium sulphate. The solvent was removed and the residue

purified by flash chromatography on silica gel with 1/2 dichloromethane/hexane as eluant to afford **5** (32 mg, 59%) as a yellow gum. R_f 0.27. IR (thin film) ν_{\max} 1960 and 1875 (CO) cm^{-1} . Mass spectrum m/e (relative intensity) 336(M^+ , 14), 280(11), 252(69), 237(3), 200(7), 94(100). ^1H NMR (CDCl_3) δ 7.42 (m, 2, ArH), 7.24 (m, 1, ArH), 7.12 (m, 2, ArH), 5.30 (m, 2, CrArH), 5.21 (m, 2, CrArH), 3.63 (s, 3, CH_3). An analytical sample was prepared by flash chromatography by use of 4/1 hexane/ether as solvent and subsequent recrystallisation from ether/hexane, m.p. 79–79.5°C. Anal. Found: C, 57.12; H, 3.60%. $\text{C}_{16}\text{H}_{12}\text{CrO}_5$ calc: C, 57.15; H, 3.60%.

In a separate experiment the structure of the intermediate complex **4** was confirmed. R_f 0.33 in 1/2 dichloromethane/hexane on silica. IR (thin film) ν_{\max} 1970 and 1890 (CO) cm^{-1} . Mass spectrum m/e (relative intensity) 342/0(M^+ , 3/8), 286/4(3/8), 258/6(15/43), 206/4(3/9), 94(6), 77(9), 52(100). ^1H NMR (CDCl_3) δ 7.47 (m, 2, ArH), 7.29 (m, 1, ArH), 7.15 (m, 2, ArH), 5.64 (m, 2, CrArH), 5.17 (m, 2, CrArH).

Phenoxybenzene(cyclopentadienyl)iron(II) hexafluorophosphate (8)

Sodium phenoxide (140 mg, 1.2 mmol) was added to a stirred, partial suspension of chlorobenzene(cyclopentadienyl)iron(II) hexafluorophosphate (**7**) (420 mg, 1.1 mmol) in deoxygenated THF (5 ml). The mixture was stirred under N_2 in the absence of light for 16 h. Most of the solvent was removed and to the residue was added a solution of ammonium hexafluorophosphate (197 mg, 1.2 mmol) in water (3 ml). The product was extracted with dichloromethane, washed with water, and dried over sodium sulphate. The solution was concentrated to 3 ml and the product precipitated by the addition of ether (20 ml). Filtration and drying in vacuo gave **8** (435 mg, 90%) as a yellow solid, m.p. 135.5–136°C. IR (Nujol mull) ν_{\max} 1650, 1590 cm^{-1} . Mass spectrum FAB m/e (relative intensity) 291($(M - \text{PF}_6)^+$, 100). ^1H NMR (acetone- d_6) δ 7.62 (t, 2, ArH), 7.44 (t, 1, ArH), 7.39 (d, 2, ArH), 6.51 (t, 2, FeArH), 6.38 (d, 2, FeArH), 6.34 (t, 1, FeArH), 5.28 (s, 5, Cp). Anal. Found: C, 46.67; H, 3.43%. $\text{C}_{17}\text{H}_{15}\text{F}_6\text{FeOP}$ calc: C, 46.82; H, 3.47%.

General procedure for the reactions of phenoxides with the tricarbonylcyclohexadienyliumiron complexes 9 and 10

The complex (1 equivalent) was added in one portion to a stirred solution of the phenoxide in dry THF at -65°C and the mixture was stirred at -65°C for 2 h. The solvent was removed under reduced pressure at -40°C and the residue extracted three times with dry ether. Removal of solvent gave essentially quantitative yields of addition products.

Tricarbonyl(1-4- η -2-methoxy-5 α -phenoxy)cyclohexa-1,3-diene)iron(0) (11)

This complex was prepared in dry acetonitrile at room temperature by reverse addition, and was recrystallised from pentane to afford yellow-green crystals, m.p. 89–90°C. IR (CHCl_3) ν_{\max} 2030, 1930, 1485 cm^{-1} . Mass spectrum m/e (relative intensity) 314 ($(M - \text{CO})^+$, 2), 286(20), 258(5), 256(20), 249(2), 200(100), 185(35), 170(95), 94(65). ^1H NMR (CDCl_3) δ 7.27–6.79 (5, m, ArH), 5.26 (1, m, 3H, $J(3,4)$ 6 Hz, $J(3,1)$ 2 Hz), 4.65 (1, m, 5H), 3.74 (3, s, OCH_3), 3.26 (1, m, 1H), 2.80 (1, m, 4H, $J(4,5)$ 4 Hz), 2.47 (1, m, 6 β H), 1.81 (1, m, 6 α H, $J(6\alpha,6\beta)$ 15 Hz), assignments were confirmed by decoupling experiments. Anal. Found: C, 56.07; H, 4.08%. $\text{C}_{16}\text{H}_{14}\text{FeO}_5$ calc: C, 56.17; H, 4.13%.

Tricarbonyl(1-4-η-2-methoxy-1-methoxycarbonyl-5α-phenoxy)cyclohexa-1,3-diene)iron(0) (12)

This complex was recrystallised from light petroleum (40–60 °C) to afford pale yellow crystals, m.p. 126–127 °C. IR (CHCl₃) ν_{\max} 2050, 1995, 1700 cm⁻¹. Mass spectrum *m/e* (relative intensity) 316((*M* - 3CO)⁺, 5), 307(10), 279(1), 251(1), 223(10), 166(35), 135(95), 94(70), 77(65), 28(100). Exact mass spectrum, found: 316.035; C₁₅H₁₆FeO₄ calc: *m/e* 316.0398. ¹H NMR (CDCl₃) δ 7.26–6.76 (5, m, ArH), 5.18 (1, d, 3H, *J* 6.5 Hz), 4.67 (1, m, 5H), 3.89 (3, s, CO₂CH₃), 3.72 (3, s, OCH₃), 2.92 (1, m, 4H), 2.76 (1, dd, 6βH, *J*(6α,6β) 14 Hz, *J*(5,6β) 11 Hz), 1.76 (1, dd, 6αH, *J*(5,6α) 2.5 Hz). Anal. Found: C, 53.68; H, 4.17. C₁₈H₁₆FeO₇ calc: C, 54.03; H, 4.03%.

Tricarbonyl(1-4-η-5α-(2,6-dibromo-4-methylphenoxy)-2-methoxycyclohexa-1,3-diene)-iron(0) (13)

This complex proved to be unstable, but characterisation was possible. ¹H NMR (CDCl₃) δ 7.3 (2, s, ArH), 5.30 (1, m, 3H), 4.74 (1, m, 5H), 3.72 (3, s, OCH₃), 3.23 (1, m, 1H), 2.65 (1, m, 4H), 2.50 (1, m, 6βH), 2.26 (3, s, CH₃), 2.15 (1, m, 6αH).

Tricarbonyl(1-4-η-5α-(2,6-dibromo-4-methylphenoxy)-2-methoxy-1-methoxycarbonyl-cyclohexa-1,3-diene)iron(0) (14)

This complex was recrystallised from diethyl ether to afford a pale yellow solid, m.p. 108–110 °C (decomp.). IR (CHCl₃) ν_{\max} 2060, 1995, 1703, 1485 cm⁻¹. Mass spectrum *m/e* (relative intensity) 307(6), 279(2), 268/6/4(27/48/27), 251(1), 223(4), 187/185(47/50), 166(25), 135(80), 133(35), 77(100). ¹H NMR (CDCl₃) δ 7.31 (2, s, ArH), 5.23 (1, d, 3H, *J*(3,4) 6.5 Hz), 4.76 (1, m, 5H), 3.90 (3, s, CO₂CH₃), 3.74 (3, s, OCH₃), 2.80 (2, m, 4 and 6βH), 2.06 (1, dd, 6αH, *J*(6α,6β) 14 Hz, *J*(5,6α) 2.5 Hz). Anal. Found: C, 39.78; H, 2.77%. C₁₉H₁₆Br₂FeO₇ calc: C, 39.90; H, 2.82%.

Tricarbonyl(1-4-η-5α-(2,6-dibromo-4-(2-methoxycarbonyl-2-trifluoroacetamidoethyl)-phenoxy)-2-methoxy-1-methoxycarbonylcyclohexa-1,3-diene)iron(0) (16)

Sodium hydride (0.158 g, 6.6 mmol) (50% dispersion in oil) was washed several times with dry light petroleum and then suspended in dry THF (20 ml). 3',5'-Dibromo-*N*-trifluoroacetyltyrosine methyl ester (**15**) (2.96 g, 6.6 mmol) was added in portions and the mixture was stirred at 25 °C for 1 h. The solvent was removed by rotary evaporation, and the resulting solid dried in vacuo. Portions of this material were used in the usual way to give the complex **16** as a pale orange solid, m.p. 74–84 °C (decomp.). IR (CHCl₃) ν_{\max} 2055, 1900, 1755, 1730, 1705, 1460 cm⁻¹. Mass spectrum *m/e* (relative intensity) 451/449/447(2/4/2), 392/390/388(2/4/2), 338/6/4(23/44/23), 267/5/3(39/100/43), 166(23). ¹H NMR (360 MHz) (CDCl₃) δ 7.24 (2, s, ArH), 6.85 (1, d, NH, *J* 8 Hz), 5.20 (1, d, 3H, *J*(3, 4) 6 Hz), 4.80 (2, m, 5H and CH), 3.90 (3, s, CO₂CH₃), 3.81 (3, s, CO₂CH₃), 3.73 (3, s, OCH₃), 3.15 (2, m, CH₂), 2.80 (2, m, 4H and 6βH), 2.10 (0.5, dd, 6αH, *J*(6α,6β) 14 Hz, *J*(5,6α) 2.5 Hz), 2.05 (0.5, dd, 6αH, *J*(6α,6β) 14 Hz, *J*(5,6α) 2.5 Hz).

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