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An iron-mediated approach to *o*-aryloxyanisoles

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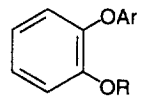
Abstract

The monomethoxylation of (1,2-dichlorobenzene)cyclopentadienyliron hexafluorophosphate, followed by phenoxylation utilizing a variety of variously substituted phenols, is shown to be an effective method for the synthesis of *o*-aryloxyanisole complexes.

Keywords: Etherification; Iron and compounds; Substitution

o-Aryloxyphenols (**1**) are important subunits in a number of notable peptides, including the vancomycin family.[1] *o*-Aryloxyanisoles (**2**) are utilized extensively as precursors to *o*-aryloxyphenols.[2-6] The standard synthesis of *o*-aryloxyanisoles by an Ullmann condensation[7] of phenols with aryl halides often leads to low yields, due to the steric and electronic effects of the *o*-methoxy group.[3-6] Nucleophilic aromatic substitution utilizing a phenoxide nucleophile and an *o*-methoxy haloarene suffers from the twin problems of a poor nucleophile and the deactivating effects of the methoxy group.[8] Furthermore, unwanted activating groups are often necessary to ensure a clean reaction.[9]



1: R = H
2: R = Me

We felt that (1,2-dihalobenzene)cyclopentadienyliron cations offered a readily available starting point for the synthesis of *o*-aryloxyanisoles. The substitution of a methoxy group for one of the chlorines has been reported by these laboratories,[10] and Pearson and coworkers have described the use of sodium alkoxides as effective nucleophiles in reactions with (chlorobenzene)cyclopentadienyliron cations.[11] We envisioned that a methoxylation/aryloxylation sequence would lead to cyclopentadienyliron complexes of *o*-aryloxyanisoles, as shown in Scheme 1. As the free *o*-aryloxyanisoles could be obtained easily by demetallation employing either pyrolytic sublimation[12] or photolysis[13,14], the pathway described can be seen as an entry to the title compounds.

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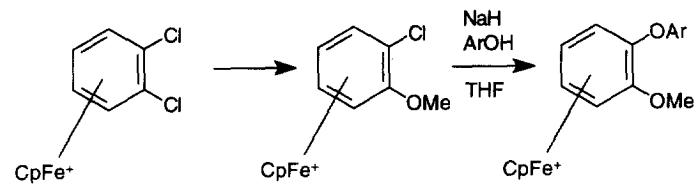
In the event, treatment of (*o*-chloroanisole)cyclopentadienyliron hexafluorophosphate with a variety of sodium phenoxides in THF at room temperature generated the desired



3 a-g

Scheme 1

	Ar	Yield (%)
3a	-C_6H_4-p-OMe	77
3b	-C_6H_4-p-tBu	94
3c	-C_6H_4-p-tAmyl	74
3d	-C_6H_4-3,4-di-Me	77
3e	-C_6H_4-3,5-di-Me	87
3f	-C_6H_4-p-Br	74
3g	-C_6H_4-p-Et	83

Table 1
Isolated yields of
o-aryloxyanisole complexes

complexes in good to excellent yields (Table 1). A general procedure is as follows: Sodium hydride (0.030g of a 60% in oil suspension, 0.73 mmol) and the phenol (0.55 mmol) were added to dry THF (15 mL) under an atmosphere of argon. After stirring for 30 min at rt, (*o*-chloroanisole) cyclopentadienyliron hexafluorophosphate[10] (150 mg, 0.37 mmol) was added in one portion. The reaction mixture was stirred for 24 h at rt, and then the solvent was removed *in vacuo*. The resulting yellow solid was partitioned between CH_2Cl_2 and water, and the organic layer was dried ($MgSO_4$) and filtered. The yellow solid remaining after removing the solvent *in vacuo* was dissolved in CH_2Cl_2 and passed through a column of neutral Al_2O_3. Recrystallization from acetone-ether yielded the product as an air-stable yellow solid. ^{13}C and ^1H NMR data of the products are shown in Table 2.

The choice of base for the deprotonation of the phenol proved to be very important, as reactions following the above general procedure employing Na_2CO_3, Et_3N and KO^{t}Bu in place of NaH all failed to produce the desired product and returned only unreacted starting

material. In the case of Na_2CO_3, reaction at reflux was also attempted, with no change in result. Although alkoxides have been shown to be poor nucleophiles in substitution reactions of (cyclopentadienyliron)chlorobenzenes when weak bases are used,[15] Adb-El-Aziz has demonstrated of the efficacy of formation of bis(aryloxycyclopentadienyliron)benzenes from dihydroxy benzenes and cyclopentadienyliron chlorobenzenes in the presence of K_2CO_3 in DMF solvent.[16] Thus, our difficulties with weak bases were unexpected.

Hindered phenoxides did not react under these conditions, as the phenoxides derived from 2,6-dimethylphenol and 2,4,6-trimethylphenol led to only unreacted starting material. Also, no *o*-aryloxyanisole was isolated from reactions employing *p*-aminophenol as the nucleophile precursor. In this case, selective deprotonation at the nitrogen prevented the formation of the required phenoxide.

Product	Ar	^{1}H NMR (acetone -d_6, 300 Mhz)	^{13}C NMR (acetone-d_6, 75 MHz)
3a	-C_6H_4-p-OMe	6.05-7.34 (m, 8H), 5.17 (s, 5H), 4.19 (s, 3H), 3.85 (s, 3H)	157.0, 147.0, 124.9, 122.7, 120.6, 114.7, 81.3, 80.6, 76.0, 75.4, 71.5, 56.6, 54.9
3b	-C_6H_4-p-tBu	6.13-7.56 (m, 8H), 5.21 (s, 5H), 4.20 (s, 3H), 1.36 (s, 9H)	171.6, 166.6, 126.5, 125.1, 118.7, 77.0, 76.2, 72.4, 70.2, 63.6, 58.4, 56.9, 30.1, 29.9
3c	-C_6H_4-p-tAmyl	6.07-7.57 (m, 8H), 5.17 (s, 5H), 4.17 (s, 3H), 2.06 (s, 3H), 1.62 (q, 2H, J= 7), 0.65 (t, 3H, J=7)	146.2, 129.4, 127.3, 125.2, 119.3, 118.5, 118.0, 115.9, 115.1, 78.5, 77.1, 76.2, 37.0, 35.7, 24.9, 7.7
3d	-C_6H_4-3,4-di-Me	6.07-7.28 (m, 7H), 5.16 (s, 5H), 4.17 (s, 3H), 2.16 (s, 6H)	151.5, 138.7, 133.5, 130.6, 125.7, 122.0, 120.0, 116.3, 83.9, 80.9, 76.7, 76.1, 71.2, 56.3, 18.2, 17.5
3e	-C_6H_4-3,5-di-Me	6.11-6.98 (m, 7H), 5.20 (s, 5H), 4.19 (s, 3H), 2.14 (s, 6H)	154.0, 139.7, 127.2, 126.1, 116.0, 82.2, 80.9, 77.5, 76.2, 71.5, 56.5, 54.8, 19.5
3f	-C_6H_4-p-Br	6.15-7.72 (m, 8H), 5.23 (s, 5H), 4.17 (s, 3H)	186.3, 180.2, 153.8, 132.5, 125.1, 120.2, 119.9, 81.1, 77.7, 76.5, 75.6, 71.2
3g	-C_6H_4-p-Et	6.20-7.43 (m, 8H), 5.22, (s, 5H), 4.21 (s, 3H), 2.67 (q, 3H, J=7), 1.28 (t, 3H, J=7)	179.0, 158.0, 141.0, 129.2, 129.1, 128.9, 119.1, 76.9, 76.8, 76.7, 76.2, 57.0, 14.3, 13.8

Table 2

^{1}H NMR and ^{13}C NMR of **3 a-g**

Despite the extensive array of methodologies utilized to synthesize them, *o*-aryloxyphenols continue to be an attractive target for synthetic chemists.[17,18,19] The appearance of *o*-aryloxyphenolic fragments in numerous important pharmacologically active compounds ensures that interest in methods to synthesize them will continue, and the challenges noted above indicate the need for new methodologies for their formation. We have described an efficient pathway to *o*-aryloxyanisoles, utilizing the easily removed cyclopentadienyliron moiety. These iron compounds are attractive precursors to *o*-aryloxyphenols; the method described therefore constitutes a novel strategy towards the synthesis of such compounds, and should be considered to be an attractive alternative to other methods.

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