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Synthesis of Aromatic Nitriles via the Temporary Complexation of Nitroarenes to the Cationic Cyclopentadienyliron Moiety

Alaa S. Abd-El-Aziz,* Waleed Boraie, and Nicole T. Gavel

Department of Chemistry, The University of Winnipeg, Winnipeg, Manitoba, Canada R3B 2E9

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Summary: Cyanide addition to cyclopentadienyliron complexes of substituted nitroarenes produced nitrile adducts where the cyano group added in the ortho position with respect to the nitro group. Cleavage of the cyclopentadienyliron moiety via oxidative demetalation with DDQ led to the isolation of functionalized aromatic nitriles in good yields.

Aromatic nitriles are important synthetic intermediates in the preparation of functionalized aromatic, heterocyclic, and polymeric materials.[1,2] One of the advantages of using the cyano functionality is its ability to extend ring systems via cyclization reactions.[3−7] Benzonitriles are especially useful as intermediates in the preparation of substituted isatoic anhydrides, which are thrombin inhibitors.[1] They can also be used as precursors in the synthesis of pesticides.[3] The preparation of this class of compounds suffers from low yields, side reactions, and harsh experimental conditions.[1−3]

It has been established that the complexation of an arene to a variety of transition-metal moieties, including those of iron, manganese, and chromium, facilitates nucleophilic aromatic substitution as well as nucleophilic addition to the ring.[8−23] Our earlier work illustrates this behavior via the introduction of the cyano group to cyclopentadienyliron complexes of aromatic ethers.[24] Recently, we were successful in the synthesis of a large number of substituted (aniline)cyclopentadienyliron complexes.[25] Time-dependent oxidations of these complexes resulted in the isolation of both the alkylnitrobenzene and acetylnitrobenzene complexes.[26] Subsequent nucleophilic addition of cyanide to the complexed arenes allowed for the preparation of novel aromatic nitriles.

Studies have shown that nucleophilic addition of hydride or carbon nucleophiles to a complexed arene usually occurs exo to the arene ring.[14,19,20] Substituent effects play a key role as to where the addition will occur. The presence of a strong electron-withdrawing group allows for addition ortho to the functional group.[27] Conversely, when the substituent is strongly electron-donating, addition occurs at the meta and para positions. In cases where preexisting substituents are in positions ortho to the nitro group, addition occurs exclusively at the unsubstituted ortho position. This can be attributed to both resonance and inductive effects and is in agreement with the rules set forth by Davies, Green, and Mingos for addition.[28]

A number of substituted cyclopentadienyliron complexes of nitroarenes were prepared and subjected to cyanide addition.[29,30] Reaction of a 7-fold excess of sodium cyanide with the nitroarene complexes **1**−**13** under mild experimental conditions produced cyclohexadienyl adducts with addition ortho to the nitro group (**14**−**26**), as described in Scheme 1. The reported yields are the result of reaction of 2 mmol of the starting complex; increasing the scale to 5 mmol of the starting complex resulted in a 10−15% decrease in yield. It is important to note that, in the case of the 4-*sec*-butylnitrobenzene complex **7**, a mixture of two diastereoisomers

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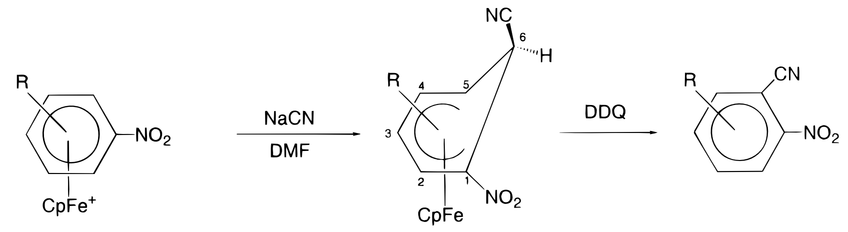
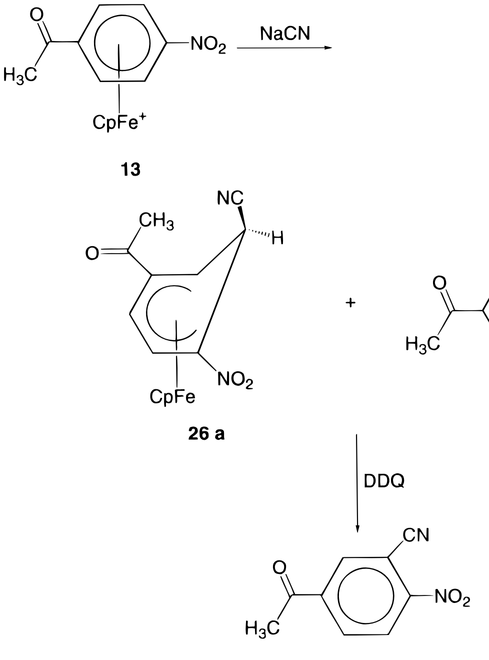
Scheme 1



1	R = 4-CH_3	**14**	72%	**27**	83%
2	R = 4-CH_2CH_3	**15**	70%	**28**	89%
3	R = 2-$CH(CH_3)_2$	**16**	60%	**29**	71%
4	R = 4-$CH(CH_3)_2$	**17**	76%	**30**	82%
5	R = 4-$CH_2CH_2CH_2CH_3$	**18**	64%	**31**	79%
6	R = 4-$C(CH_3)_3$	**19**	61%	**32**	76%
7	R = 4-$CH(CH_3)CH_2CH_3$	**20 a,b**	65%	**33**	69%
8	R = 4-$CH_2CH_2CH_2CH_2CH_3$	**21**	76%	**34**	75%
9	R = 2,3-$(CH_3)_2$	**22**	69%	**35**	71%
10	R = 2,4-$(CH_3)_2$	**23**	74%	**36**	76%
11	R = 3,4-$(CH_3)_2$	**24**	67%	**37**	79%
12	R = 3,5-$(CH_3)_2$	**25**	68%	**38**	82%

Scheme 2



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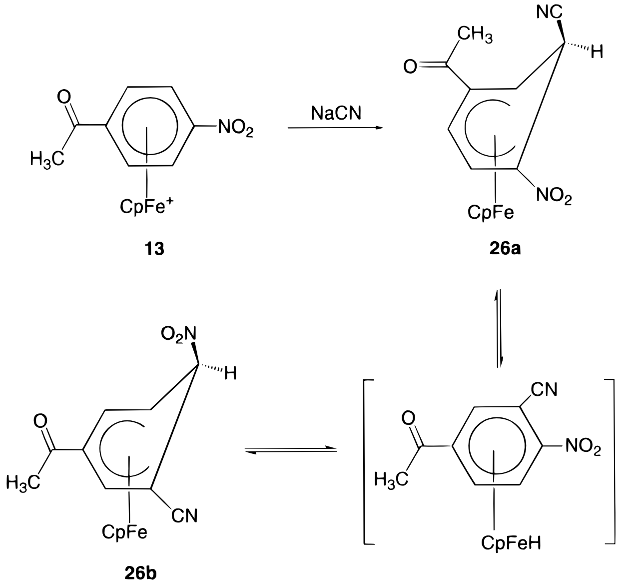
Scheme 3



was obtained. The ^1H and ^{13}C NMR data for all of the cyclohexadienyl adducts, which are consistent with previous findings, are available in the Supporting Information.[22−24] A significant observation is the upfield shift of the cyclopentadienyl protons from approximately 5.44−5.54 ppm in the starting complexes to 4.38−4.58 ppm in the adducts.

Although addition occurred ortho to the nitro group when one electron-withdrawing group was present on the ring, two electron-withdrawing groups allowed for the isolation of two adducts (**26a,b**), as illustrated in Scheme 2. Cyanide addition to **13** resulted in the formation of isomers **26a** and **26b**; one of the isomers resulted from addition to the ortho position (**26a**) and the other from a subsequent hydrogen transfer to the cyclopentadienyliron ligand followed by addition to the carbon atom ipso to the nitro group (**26b**), as shown in Scheme 3. This type of hydrogen transfer has been reported previously for arenes coordinated to other metallic systems.[31−34] These structures were confirmed using ^1H and ^{13}C NMR. Characterization of the individual isomers was accomplished using HH and CH COSY NMR. Subsequent removal of the metallic moiety led to the isolation of only one isomer (**39**), which supports the structures of the proposed adducts.

The oxidative demetalation of the cyclohexadienyl adducts with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) allowed for the isolation of the aromatic nitriles **27**−**39** in very good yields. The most important features of the ^1H NMR spectra are the absence of the cyclopentadienyl resonances and the downfield shifts of the aromatic protons. These spectral shifts represent the loss of coordination to the cyclopentadienyliron moiety and rearomatization to the benzonitrile. The structures

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of all aromatic nitriles were supported by ^1H and ^{13}C NMR, IR, mass spectroscopy, and elemental analysis, as listed in the Supporting Information.

In conclusion, the cyclopentadienyliron moiety facilitated the nucleophilic addition of the cyano group to the complexed ring system. The cyanide anion added ortho to the electron-withdrawing groups, and demetalation afforded the aromatic nitriles in good yields. This represents a new, milder method for the synthesis of this class of compounds.

Experimental Section

The starting complexes **1**−**13** were made according to established procedures.[25,26] Sodium cyanide, DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), dimethylformamide, dichloromethane, chloroform, and acetonitrile are available commercially and were used without further purification. Silica gel (60−100 mesh) was used in the chromatographic purification of the demetalated product.

^1H (200 MHz) and ^{13}C (50 MHz) NMR spectra were recorded on a Varian Gemini 200 spectrophotometer. The chemical shifts for all species are given relative to the solvent, and coupling constants were measured in hertz (Hz). IR spectra were recorded on a Bomem MB 102 FT-IR spectrophotometer.

Preparation of the Cyanide Adducts 14−**26**. The starting complex (2 mmol) was combined with NaCN (14 mmol) in a 25 mL round-bottom flask equipped with a magnetic stir bar. The two solids were dissolved in 4 mL of DMF, after which 2 drops of distilled water were added. The reaction mixture was stirred for 0.5 h under a nitrogen atmosphere. The solution was then poured into water and extracted three times with chloroform. The organic fraction was then washed several times with water and dried over anhydrous magnesium sulfate. Rotary evaporation of the solvent yielded the desired product.

Oxidative Demetalation (27−**39)**. The adduct (2 mmol) was initially dissolved in 4 mL of acetonitrile, after which DDQ (4 mmol) was added. This mixture was then stirred for 0.5 h. After this time, the solvent was removed by rotary evaporation, leaving a purple solid. Dissolution of this material into dichloromethane (1 mL) allowed for its introduction onto a short silica gel/hexane column. Chloroform was used to elute the desired free arene. Rotary evaporation of the chloroform allowed for the isolation of the nitrile compound.

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Supporting Information Available: Tables of NMR, IR, elemental analysis, and mass spectroscopy data for adducts **14**−**39**. This material is available free of charge via the Internet at http://pubs.acs.org.

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