Regioselective Nitrile Addition to Hindered Tricarbonylcyclohexadienyliumiron Complexes and Spirolactone Formation

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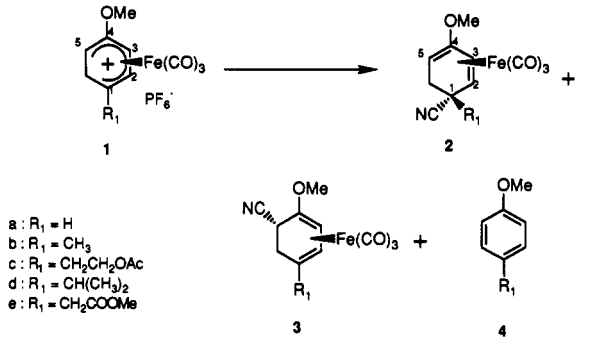
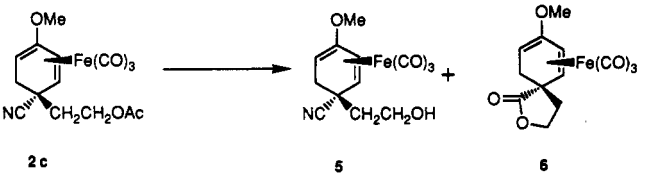
Summary: By using a large excess of trimethylsilyl cyanide and a short reaction time, trimethyl isocyanide in sufficient amount is generated and added regioselectively at the C-1 terminus of the tricarbonyl cyclohexadienylium species 1, irrespective of steric hindrance and its α-proton acidity. Formation of the aromatic and trienyl complex is suppressed. Upon saponification or hydrolysis, addition product 2c is converted into the synthetically useful spirolactone 6. For the reaction mechanism, formation of phosphorus pentafluoride, trimethylsilyl fluoride, and free cyanide during the reaction between hexafluorophosphate anion and trimethylsilyl cyanide is suggested.

Tricarbonylcyclohexadienyliumiron complexes have received increasing attention for their ability to react with a wide variety of nucleophiles which have led to their application as key intermediates in organic synthesis.[1] Unfortunately, substitution at the C-1 terminus of complexes 1 severely limits the range of suitable nucleophiles,



since in many cases competing deprotonation results in the formation of trienyl complexes,[2] together with decreasing regioselectivity.[3] The metal cyanide anion has been used successfully only for unsubstituted C-1 dienylium complexes.[4] Recently, it has been reported[5] that trimethylsilyl cyanide is a reagent far superior to the metal cyanide. The scope for using trimethylsilyl cyanide has not been tested beyond the methyl substitution at C-1 of the dienylium complex 1.

We were interested in overcoming the limitation by steric effect of reaction of complexes of type 1 with cyanide anion. We now describe the results of studies designed to explore the synthetic potential and mechanistic implication of this reaction. The ability to effect cyanide addition regioselectively at the C-1 terminus of complex **1c** will lead to the facile construction of the spirolactone **6** upon hydrolysis, a valuable synthetic intermediate.



Results and Discussion

The cyclohexadienylium complex **1c** was prepared according to the method of Pearson.[6] The reaction of **1c** with potassium cyanide was found to give poor yields of **2c**, together with a small amount of regioisomer **3c** and an aromatic product. Increasing the amount of potassium cyanide and using a longer reaction time have an adverse effect on the reaction, giving decreased regioselectivity with formation of equal amounts of **2c** and **3c**, together with the aromatic compound. Consequently, we turned our attention to the use of trimethylsilyl cyanide. Reaction of **1c** under the reported conditions[5] was found to yield a useful quantity of **2c** with good regiocontrol. Unexpectedly, an initial attempt to improve the yield of **3c** by a prolonged reaction time was unsuccessful; instead, aromatized products began to appear. In fact, the reaction of **1c** with trimethylsilyl cyanide takes place only at elevated temperatures, due to the deactivating influence of the methoxy group. We thus conclude that the critical factors in this reaction are the higher concentration of trimethylsilyl cyanide and a shorter reaction time. Our results in Table I show that the best yield of **2c** could be achieved with 10 equiv of trimethylsilyl cyanide in refluxing acetonitrile for 4 h. A further increase in the concentration of trimethylsilyl cyanide has no marked influence on the reaction. We next needed to examine the product distribution for the reaction of **1c** with low concentrations of trimethylsilyl cyanide. When **1c** was reacted with 1.5 equiv of trimethylsilyl cyanide, after the mixture was refluxed for 3 h it produced selectively **2c**, albeit in poor yield. Refluxing for 7 h improved the yield of **2c** slightly, and prolonged refluxing for 20 h decreased the yield of **2c** but favored the formation of aromatic products. These results indicate that the synthetic value of this reaction could be improved if the appropriate excess of the required reagent to effect conversion in a specified period of time could be determined.

Stephenson[7] has reported that, for all but the most unreactive dienylium complexes, the preequilibrium step between trimethylsilyl cyanide and isocyanide is rate-

(1) Pearson, A. J. *Pure Appl. Chem.* **1983**, *55*, 1767.
(2) Pearson, A. J. *J. Chem. Soc., Perkin Trans. 1* **1978**, 495.
(3) Pearson, A. J.; Ham, P.; Ong, C. W.; Perrior, T. R.; Rees, D. C. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1525.
(4) Pearson, A. J.; Chardler, M. *J. Organomet. Chem.* **1980**, *202*, 175.
(5) Alexander, R. P.; Stephenson, G. R. *J. Organomet. Chem.* **1986**, *299*, C-1.
(6) Pearson, A. J.; Chandler, M. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2238.
(7) Alexander, R. P.; James, T. D.; Stephenson, G. R. *J. Chem. Soc., Dalton Trans.* **1987**, 2013.

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Table I. Reaction Conditions for (TMS)CN and KCN Addition to Cyclohexadienylium Salt 1

compd	amt of cyanide, equiv	solvent	reacn conditions	product yield[a]
1c	1.5 ((TMS)CN)	CH_3CN	reflux, 3 h	2c (20), 3c (0), 4 (0)
1c	1.5 ((TMS)CN)	CH_3CN	reflux, 7 h	2c (29), 3c (0), 4 (0)
1c	1.5 ((TMS)CN)	CH_3CN	reflux, 20 h	2c (10), 3c (0), 4 (40)
1c	5.0 ((TMS)CN)	CH_3CN	reflux, 4 h	2c (35), 3c (0), 4 (0)
1c	5.0 ((TMS)CN)	CH_3CN	room temp, 16 h	2c (45), 3c (0), 4, (10)
1c	10.0 ((TMS)CN)	CH_3CN	reflux, 4 h	2c (71), 3c (8), 4 (0)
1c	20.0 ((TMS)CN)	CH_3CN	reflux, 4 h	2c (73), 3c (8), 4 (0)
1c	(TMS)CN/$Bu_4N^+F^-$	CH_3CN	0 °C, 1 h	2c (18), 3c (8), 4 (10)
1c	(TMS)CN/$Bu_4N^+F^-$	CH_3CN	0 °C, 16 h	2c (25), 3c (30), 4 (40)
1d	10.0 ((TMS)CN	CH_3CN	reflux, 4 h	2d (62), 3d (0), 4 (0)
1e	10.0 ((TMS)CN	CH_3CN	reflux, 4 h	2e (40), 3e (10), 4[b] (25)
1c	2 (KCN)	acetone/H_2O	0 °C, 1 h	2c (20), 3c (5), 4 (8)
1c	4 (KCN)	acetone/H_2O	0 °C, 16 h	2c (28), 3c (28), 4 (42)
1d	2 (KCN)	acetone/H_2O	0 °C, 1 h	2d (5), 3d (10), 4 (35)
1e	2 (KCN)	acetone/H_2O	0 °C, 1 h	2e (–), 3e (–), 4[b]

[a] Yield obtained from starting dienylium salt. Unreacted dienylium salt may be recovered by filtration. Percent yields are given in parentheses. [b] Also obtained as the trienyl complex.[6]

limiting (eq 1). The presence of steric hindrance at the

$$\mathrm{TMS{-}C{\equiv}N} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{TMS{-}N^+{\equiv}C^-} + 1 \xrightarrow{k_2} 2 + 3 \quad (1)$$

$$\mathrm{PF_6^-} \rightleftharpoons \mathrm{PF_5} + \mathrm{F^-}$$

C-1 terminus and deactivation by the methoxy group in **1c** has shifted the reaction toward the formation of aromatized product in higher yield. The mechanism outlined previously does not reflect on the formation of aromatized product. A second reaction pathway (eq 2)

$$\therefore\ \mathrm{TMS{-}C{\equiv}N} + \mathrm{Fe(CO)_3{-}(dienylium)^+PF_6^-} \longrightarrow$$

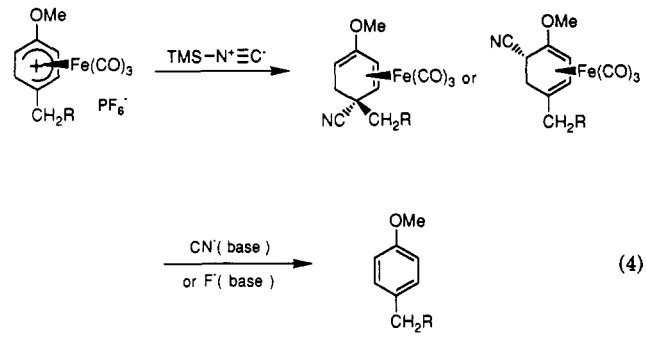
$$\mathrm{TMS{-}F} + \mathrm{PF_5} + \mathrm{CN^-\ (base)} + 1 \longrightarrow 2 + 3 + 5 \quad (2)$$

which involved the reaction of trimethylsilyl cyanide with the hexafluorophosphate anion to generate trimethylsilyl fluoride, phosphorus pentafluoride, and free cyanide ion may take place, which accounts for the formation of aromatized product. The decomposition of hexafluorophosphate anion to phosphorus pentafluoride and fluoride anion at comparatively low temperature has been reported[8] in the formation of 1-chloro-4-fluorobenzene from (*p*-chlorophenyl)diazonium hexafluorophosphate. The release of fluoride anion, which in turn reacts with trimethylsilyl cyanide to give basic cyanide anion, is expected to give poorer regioselectivity and aromatic product with **1c**, similar to the case observed for reaction with potassium cyanide. Variation of the excess of trimethylsilyl cyanide indicates that the ratio of products obtained is proportional to the concentration of trimethylsilyl isocyanide and free cyanide ion present in the reaction mixture. Our work indicates that the concentration of trimethylsilyl isocyanide must be high enough for rapid addition to the dienylium complex prior to the dissociation of hexafluorophosphate anion to generate the fluoride anion followed by cyanide anion. This phenomenon may also account for the formation of the aromatic product after prolonged reaction time. It is suggested that the free fluoride and cyanide anions generated after prolonged reaction cause dehydrocyanation of the product **2c** and **3c** to give the aromatic product (eq 3). The postulated reaction between the hexafluorophosphate anion and trimethylsilyl cyanide may be easily mimicked using tetrabutylammonium

$$\mathrm{TMS{-}C{\equiv}N} + \mathrm{Bu_4N^+F^-} \longrightarrow$$

$$\mathrm{TMS{-}F} + \mathrm{Bu_4^+} + \mathrm{CN^-\ (base)} + 1 \longrightarrow 2 + 3 + 5 \quad (3)$$

fluoride. Tetrabutylammonium fluoride is a widely used reagent for the desilylation of silyl enol ethers. As anticipated, the reaction of **1c** with trimethylsilyl cyanide and tetrabutylammonium fluoride was found to give poorer regioselectivity, lower yields of **2c** and **3c**, and aromatized product even at lower temperature and shorter reaction time, which is consistent with our proposed mechanim (eq 4).



(4)

We next turn our attention to the series of hindered cyclohexadienylium complexes **1d,e**, and the results are summarized in Table I. Reaction of **1d** with trimethylsilyl cyanide (10 equiv) under reflux for 4 h was found to give exclusively **2c** in high yield. Conversely, reaction of **1d** with potassium cyanide was found to give very poor yields of **2c** and **3c**, but mainly aromatic products. The increase in α-proton acidity in **1e** did not hamper nitrile addition with trimethylsilyl cyanide. A reasonable yield of **2e** was obtained in this case, with increasing amounts of trienyl and aromatized products.

Next we investigated the spirolactonization of complex **2d**. Table II summarizes the results of studies for the conversion of **2d** to spirolactone **6** under both basic and acidic conditions. It became apparent that these reactions favored the simple saponification of the acetate to the corresponding alcohol **5** in a shorter reaction time. A high yield of the spirolactone **6** was eventually obtained after prolonged acid hydrolysis of the acetate, formed by the intramolecular condensation of the hydroxy complex **5** with the nitrile to give an imine which was further hydrolyzed to the ketone.

There are two noteworthy features of these results. First, the yields obtained during nitrile addition to the

(8) Corbridge, D. E. C. *Phosphorus: An outline of its Chemistry, Biochemistry and Technology*, 3rd Ed.; Elsevier: Amsterdam, 1985; p 102.

Table II. Hydrolysis of Complex 2c under Basic and Acidic Conditions

hydrolysis conditions	temp	reacn time	yield, % 5	6
K_2CO_3 (1.02 equiv)/MeOH	0 °C	30 min	65	15
K_2CO_3 (1.02 equiv)/MeOH	0 °C	2 h	15	37
K_2CO_3 (1.02 equiv)/MeOH	room temp	15 h	4	64
H_2SO_4 (cat.)/MeOH	room temp	9 h	19	44
H_2SO_4 (cat.)/MeOH	room temp	1 day	0	76
NaOMe (1 equiv)/THF/MeOH	0 °C	30 min	32	16
NaOMe (1 equiv)/THF/MeOH	−78 °C		0	0

cyclohexadienylium complex are generally high with minimum proton abstraction, irrespective of the substituents at the C-1 terminus in 1. Second, the regioselectivity during the reaction is more pronounced, which gives mainly the desired C-1 addition product. The results presented here indicate that significant changes in reactivity occur when a large excess of trimethylsilyl cyanide is used together with a shorter reaction time. A clear understanding of all the reaction pathways among the reagents involved can lead to successful modifications of the reaction in favor of the required product.

Experimental Section

The organoiron complexes **1c**,[6] **1d**,[9] and **1e**[6] were prepared using published methods. Acetonitrile was distilled from calcium hydride under nitrogen. IR spectra were measured with a Digilab FTS-40 spectrometer. ^{1}H NMR spectra were obtained using a Varian VXR-300 (300 MHz) spectrometer. Chemical shifts are reported in ppm relative to TMS. Mass spectra were obtained using a Hitachi m-52 spectrometer. Elemental analyses were performed using a Heraeus CHNO-rapid analyzer. Radial chromatography was performed on a Harrison Research Chromatotron using 2.0 mm layer thickness silica gel 60FP-254 with calcium sulfate binder.

General Procedure for Nitrile Addition to the Tricarbonyl Cyclohexadienylium Salt. (a) Sodium Cyanide Method. To a stirred solution of potassium cyanide in 20% aqueous acetone at 0 °C under nitrogen was added the hexafluorophosphate salt in acetone. The reaction was carried out for the period indicated in Table I, and the mixture was then poured into ethyl acetate and washed successively with brine, cold 5% hydrochloric acid, aqueous sodium bicarbonate, and water. The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure to give crude products. The mixture was separated by radial chromatography using hexane/ethyl acetate (5:1) as eluent.

(b) Trimethylsilyl Cyanide Method. Trimethylsilyl cyanide was added to a stirred solution of the hexafluorophosphate salt in acetonitrile and refluxed for a given period. The reaction mixture was cooled to room temperature and poured into water. The product was extracted with ethyl acetate and washed with brine and water. The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure to give a crude product. It was purified as above.

Compounds **2c**, **3c**, and **2e** were obtained as yellowish orange oils, whereas **2d** was obtained as a yellow solid.

Tricarbonyl[2-acetoxy-1-((2-5-η)-1-cyano-4-methoxycyclohexa-2,4-dienyl)ethane]iron (2c): ν_{max} ($CHCl_3$) 2231, 2061, 1981, 1732, 1485 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.18 (1 H, dd, J = 6.3 and 1.8 Hz, 3-H), 4.24 (2 H, t, J = 6.6 Hz, CH_2OAc), 3.69 (3 H, s, OMe), 3.48 (1 H, m, 5-H), 2.66 (1 H, d, J = 6.3 Hz, 2-H), 2.39 (1 H, dd, J = 15.6 and 3 Hz, endo 6-H), 2.06 (3 H, s, OAc), 2.1–1.8 (2 H, obscured, CH_2), 1.84 (1 H, dd, J = 15.6 and 3 Hz, exo 6-H); mass m/e 361 (M^+), 335 (M^+ − CN), 305 (M^+ − 2CO). Anal. Calcd for $C_{15}H_{15}NO_6Fe$: C, 49.89; H, 4.19; N, 3.88. Found: C, 50.08; H, 4.23; N, 4.01.

(9) Prepared according to: Pearson, A. J.; Perrior, T. R. *J. Organomet. Chem.* **1985**, *285*, 254 (for the methoxy-substituted complex).

Tricarbonyl[(2,5-η)-2-methoxy-5-(2-acetoxyethyl)cyclohexa-2,4-dienyl cyanide]iron (3c): ν_{max} ($CHCl_3$) 2234, 2048, 1980, 1736 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.41 (1 H, d, J = 4.0 Hz, 3-H), 5.14 (1 H, d, J = 4.0 Hz, 4-H), 4.14 (2 H, t, J = 6 Hz, CH_2OAc), 3.49 (3 H, s, OMe), 3.39 (1 H, dd, J = 11.0 and 10.0 Hz, 1-H), 2.34 (1 H, dd, J = 15.0 and 11.0 Hz, endo 6-H), 2.10 (3 H, s, OAc), 2.03 (2 H, obscure, CH_2); mass m/e 361 (M^+), 335 (M^+ − CN), 305 (M^+ − 2CO), 277 (M^+ − 3CO).

Tricarbonyl[1-((2-5-η)-1-cyano-4-methoxycyclohexa-2,4-dienyl)-1-methylethane]iron (2d): mp 101–102 °C; ν_{max} ($CHCl_3$) 2226, 2055, 1986, 1490 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.78 (1 H, dd, J = 6.3 and 2.4 Hz, 3-H), 3.68 (3 H, s, OMe), 3.48 (1 H, m, 5-H), 2.73 (1 H, d, J = 6.3 Hz, 2-H), 2.31 (1 H, dd, J = 16.0 and 4.0 Hz, endo 6-H), 1.80 (1 H, dd, J = 16.0 and 4.0 Hz, exo 6-H), 1.54 (1 H, hept, J = 6.3 Hz, $CHMe_2$); mass m/e 317 (M^+), 291 (M^+ − CN), 289 (M^+ − CO), 263 (M^+ − CO − CN). Anal. Calcd for $C_{14}H_{15}NO_4Fe$: C, 53.02; H, 4.77; N, 4.42. Found: C, 52.98; H, 4.80; N, 4.40.

Tricarbonyl[methyl ((2-5-η)-1-cyano-4-methoxycyclohexa-2,4-dienyl)acetate]iron (2e): ν_{max} ($CHCl_3$) 2235, 2060, 1993, 1743 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.13 (1 H, dd, J = 6.3 and 2.4 Hz, 3-H), 3.73 (3 H, s, COOMe), 3.70 (3 H, s, OMe), 3.46 (1 H, m, 5-H), 2.74 (1 H, d, J = 6.3 Hz, 2-H), 2.67 (2 H, s, CH_2COOMe), 2.50 (1 H, dd, J = 15.0 and 3.0 Hz, endo 6-H), 1.82 (1 H, dd, J = 15.0 and 3.0 Hz, exo 6-H); mass m/e 319 (M^+ − CO), 291 (M^+ − 2CO), 263 (M^+ − 3CO). Anal. Calcd for $C_{14}H_{13}NO_6Fe$: C, 48.44; H, 3.78; N, 4.04. Found: C, 48.40; H, 3.75; N, 4.00.

Basic Hydrolysis. To a stirred solution of potassium carbonate (1.02 equiv) in methanol at 0 °C was added **1d**. The reaction mixture was stirred at 0 °C for the time indicated in Table II, after which it was neutralized with acetic acid. The solvents were evaporated, the residue was dissolved in ether, and this solution was washed successively with water and brine and dried (Na_2SO_4). The crude product was chromatographed on a silica gel column (with petroleum ether/ethyl acetate (4:1) as eluent) to afford **5** and **6**.

Acidic Hydrolysis. To a stirred solution of concentrated sulfuric acid (catalytic amount) in methanol was added **1d**. The reaction mixture was stirred at room temperature for 1 day, after which it was neutralized with a dilute solution of sodium bicarbonate. The solvents were evaporated, the residue was dissolved in ether, and this solution was washed successively with water and brine and dried (Na_2SO_4). Pure **6** was obtained in 76% yield.

Compound **5** was obtained as a yellowish orange gum, and **6** was obtained as a yellow solid.

Tricarbonyl[(6,9-η)-1-oxo-8-methoxy-2-oxaspiro[4.5]deca-6,8-diene]iron (6): mp 144–145 °C: ν_{max} ($CHCl_3$) 2050, 1985, 1760, 1490 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.10 (1 H, dd, J = 6.3 and 2.4 Hz, 3-H), 4.25 (2 H, m, CH_2O–), 3.68 (3 H, s, OMe), 3.49 (1 H, m, 5-H), 2.51 (1 H, d, J = 6.3 Hz, 2-H), 2.23 (1 H, dd, J = 15.0 and 3.0 Hz, endo 6-H), 2.28 (1 H, m, –CH_2), 2.08 (1 H, m, CH_2), 1.75 (1 H, dd, J = 15.0 and 3.0 Hz, exo 6-H); mass m/e 320 (M^+), 292 (M^+ − CO), 264 (M^+ − 2CO), 236 (M^+ − 3CO). Anal. Calcd for $C_{12}H_{12}O_6Fe$: C, 48.78; H, 3.75. Found: C, 48.74; H, 3.75.

Tricarbonyl[((2-5-η)-1-cyano-4-methoxycyclohexa-2,4-dienyl)ethanol]iron (5): ν_{max} ($CHCl_3$) 3620, 2223, 2057, 1990, 1491 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.17 (1 H, dd, J = 6.3 and 2.5 Hz, 3-H), 3.87 (2 H, t, J = 6 Hz, CH_2OH), 3.69 (3 H, s, OMe), 3.47 (1 H, m, 5-H), 2.72 (1 H, d, J = 6.3 Hz, 2-H), 2.52 (1 H, dd, J = 15.0 and 3.0 Hz, endo 6-H), 2.10–1.70 (4 H, CH_2, exo 6-H and OH exchangeable with D_2O).

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