Tricarbonylcyclohexadienyliumiron Complexes in the Synthesis of 2-Azaspiro[5.5]undecane System with Tunable Amide

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Excellent regio- and stereoselectivity during nitrile addition to dienylium-$Fe(CO)_3$ can be achieved with perchlorate salts, allowing the preparation of the 1-oxo- and 3-oxo-2-azaspiro[5.5]undecane ring systems. The phthalimide complex **2** was prepared in high yield by Mitsunobo reaction.

The creation of spirolactam centers is one of the more challenging problems in organic synthesis. A variety of spirocycles are readily accessible with tricarbonylcyclohexadienyliron chemistry, including spiro[4.5]decane,[1] spiro[5.5]undecane,[2] 1-azaspiro[4.5]decane,[3] 1-azaspiro-[5.5]undecane,[4] 2-oxo- and 2-azaspiro[4.5]decane.[5] Recently, we described the high yield formation of spirolactone by cyanide addition to tricarbonylcyclohexadienylium iron complexes.[6] We now report a unique iron-mediated method for the synthesis of the 2-azaspiro[5.5]-undecane system with a tunable amide position, starting from a common precursor. The 2-azaspiro[5.5]undecane is an important intermediate in the synthesis of *Nitraria* alkaloids[7a−c] which exhibit marked neurophysiological activity.

The starting material for our synthesis was the ester complex **1**, which was readily prepared from 4-methoxycinnamic acid.[8] The ester complex **1** was smoothly reduced to the alcohol complex **2** with diisobutylaluminum hydride. The alcohol complex **2** has been previously converted into the phthalimido complex **3** in a two step sequence of tosylation followed by displacement with potassium phthalimide.[9] The use of excess toluene-4-sulfonyl chloride has been reported to cause considerable decomposition of the complex during work up. We chose a direct formation of the phthalimido complex **3** (80% yield) by means of a Mitsunobu reaction[10] of the alcohol complex **2** and phthalimide. This methodology overcame the previous problem of tosylation. The phthalimido complex **3** when treated with triphenylmethylium perchlorate[11] underwent regiospecific hydride abstraction to give the dienylium salt **4a**. The reaction of the dienylium hexafluorophosphate salt **4b** with various nucleophiles has been reported[12] to give a mixture of regioisomers from attacks at each dienylium terminus C-1 and C-5. We have demonstrated the ability of trimethylsilyl cyanide to add regioselectively to a highly-substituted dienylium perchlorate salt.[10] As anticipated, the perchlorate salt **4a** reacts regioselectively with trimethylsilyl cyanide with attack at the more substituted terminus, and stereoselectively opposite to the $Fe(CO)_3$ group to give complex **5** in 86% yield. This again demonstrates the dual advantages of perchlorate counteranion, good regioselectivity and high yields of cyanide addition products.

A number of options presented themselves for the conversion of complex **5** into the appropriate 2-aza-1-oxospiro[5.5]undecane system (Scheme 1). Preliminary trials indicated that selective deprotection of the phthalimide to release the amine with hydrazine, in the presence of the cyanide functionality, can be efficiently carried out in 70% yield to give the amine−cyanide complex **6**. We were now in a position to examine the direct formation of the spirolactam complex **7**. We have previously shown that alcohol-cyanide complex can be readily converted into the lactone with acid.[6] However, the reaction of amine-cyanide complex **6** under acidic condition (catalytic concentrated sulfuric acid) and Lewis acid (BF_3-etherate) disappointingly did not effect cyclization into the appropriate spirolactam **7**. It became apparent that spirolactam formation might be more facile under basic conditions. Treatment of the amino−cyanide complex **6** with saturated potassium carbonate solution in ethanol was found to give a high yield (75%) of the cyclized spirolactam complex **7**.

In order to increase the functionalizable positions of the spirolactam complex, we next examined the synthesis of the 2-aza-3-oxospiro[5.5]undecane ring system (Scheme 2) starting from the common complex **1**. The synthesis of a tunable amide funtionality through this common precursor should increase its flexibility for applications in synthesis. Hydride abstraction of the ester complex **1** with triphenylmethylium perchlorate again took place regioselectively to give the dienylium perchlorate salt **8**. The perchlorate salt **8**, as expected, underwent regio- and stereoselective addition with trimethylsilyl cyanide at the more substituted terminus to give **9** in 75% yield. Our strategy involved the selective conversion of the cyanide group into an amine, followed by an intramolecular condensation with the ester to form the spirolactam. Reduction of the cyanide group in the complex **9** to a methylene amine unit in the presence of an ester could only be achieved by using hydrogenation, and this proved troublesome with platinum or palladium catalysts. The cyanide group was eventually reduced to the methylene

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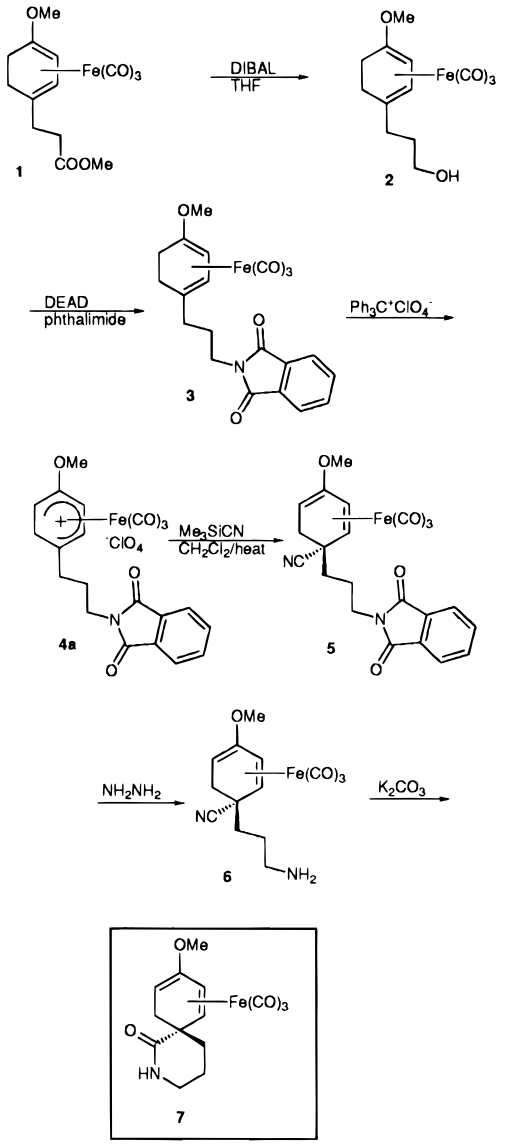
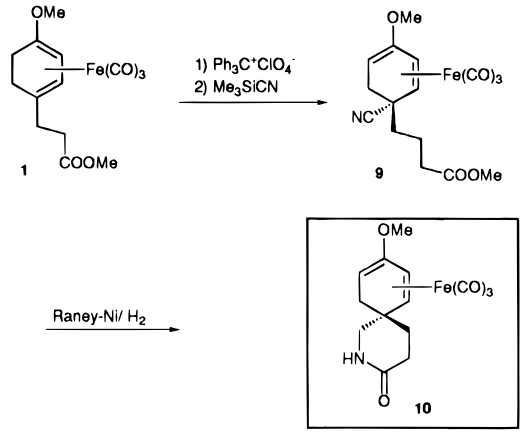
Scheme 1. 1-Oxo-2-azaspiro[5.5]undecane



Scheme 2. Synthesis of 3-Oxo-2-azaspiro[5.5]undecane



amine using Raney nickel, which cyclized spontaneously to the 2-aza-3-oxospirolactam **10** in very high yield (96%). One feature of spirolactam complex **10** is that the α-carboamide proton which is acidic may be removed by base for the introduction of a substituent.

In summary, the regioselective addition of a nitrile group to a variety of dienylium perchlorate salts in high yield has allowed us to develop two flexible approaches to 2-azaspiro[5.5]undecane with tunable amide groups. This sequence constitutes a new and general synthetic methodology available for the syntheis of spirolactam.

Experimental Section

The organoiron complexes **1** and **2** were prepared using the published method.[1] Melting points are uncorrected. All preparative and chromatographic operations were conducted under a nitrogen atmosphere.

Tricarbonyl{1−4-*η*-[1-methoxy-4-(3-phthalimidopropyl)-cyclohexa-1,3-diene]}iron (3). Diethyl azodicarboxylate (2.38 mL), triphenylphosphine (4.26 g), and phthalimide (2.39 g) were dissolved in THF (100 mL), and the alcohol complex **2** (5.00 g) was added with stirring at room temperature. After the solution was kept standing overnight, the solvent was filtered and removed with a rotatory evaporator. The residue was chromatographed on a silica gel column, eluting with hexane:ethyl acetate (5:1) to give the desired product **3**[9] in 80% yield (5.67 g). IR (KBr) ν_{max} 2140, 1965, 1772, 1712 cm^{-1}. ^{1}H NMR δ ($CDCl_3$) 7.87−7.86 (4H, m), 5.16 (1H, d, J = 4.5 Hz), 4.94 (1H, d, J = 4.5 Hz), 3.65 (2H, t), 3.44 (3H, s), 2.60−1.50 (8H, m).

Tricarbonyl{1−5-*η*-[2-methoxy-5-(3-phthalimidopropyl)-cyclohexa-2,4-dienylium]}iron Perchlorate (4a). Triphenylmethylium perchlorate (6.27 g) was added to a solution of the phthalimide complex **3** (8.25 g) in dichloromethane (150 mL) and stirred at room temperature for 4 h. Most of the solvent was removed under reduced presure, and dry ether was added (40 mL) to give the bright yellowish perchlorate complex **4a** in 90% yield (8.99 g). IR (KBr) ν_{max} 2364, 2338, 1760, 1716 cm^{-1}. ^{1}H NMR δ (CD_3CN) 7.94−7.86 (4H, m), 6.88 (1H, dd, J = 6.0 and 2.6 Hz), 5.74 (1H, d, J = 6.0 Hz), 5.74 (1H, d, J = 6.0 Hz), 3.99−3.97 (1H, m), 3.86 (3H, s), 3.71 (2H, t), 3.08 (1H, dd, J = 15.8 and 6.0 Hz), 2.41 (1H, d, J = 15.8 Hz), 2.30−1.60 (4H, m).

1−4-*η*-[5-Cyano-2-methoxy-5-(3-phthalimidopropyl)cyclohexa-1,3-diene]tricarbonyliron (5). The perchlorate salt **4a** (1.20 g) was dissolved in dichloromethane (120 mL) under nitrogen and Me_3SiCN (3.00 mL) added dropwise at room temperature. The reaction mixture was refluxed overnight after which it was allowed to cool. The reaction mixture was poured into a cold solution of sodium metabisulfite and the organic layer separated and washed with water and brine. The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure to give the cyanide adduct **5** (0.90 g) as a yellow-greenish gum in 86% yield. IR ($CHCl_3$) ν_{max} 2227, 2050, 1979, 1771, 1713 cm^{-1}. ^{1}H NMR δ ($CDCl_3$) 7.85−7.67 (4H, m), 5.13 (1H, dd, J = 6.4 and 2.5 Hz), 3.74 (2H, t), 3.66 (3H, s), 3.42 (1H, m), 2.58 (1H, d, J = 6.4 Hz), 2.31 (1H, dd, J = 15.0 and 2.5 Hz), 1.90−1.30 (5H, m); *m/e* 462 (M^+), 434, 406, 378. Calcd for $C_{22}H_{18}N_2O_6Fe$: C, 57.17; H, 3.90; N, 6.06. Found: C, 56.94; H, 3.78, N, 5.88.

1,4-*η*-[5-Cyano-5-(3-aminopropyl)-2-methoxycyclohexa-1,3-diene]tricarbonyliron (6). The complex **5** (1.07 g) and hydrazine hydrate (1 mL) in methanol were stirred at room temperature overnight. The methanol was removed and the residue extracted with chloroform. The combined extracts were dried (Na_2SO_4) and evaporated to give the amine complex **5**, which was further purified by chromatogaphy on a silica gel column using chloroform:methanol (10:1) as eluent. This gave the pure amine complex **6** as a yellowish gum in 70% yield. IR ($CHCl_3$) ν_{max} 3372, 3296, 2226, 2057, 1919 cm^{-1}. ^{1}H NMR δ ($CDCl_3$) 5.17 (1H, dd, J = 6.4 and 2.5 Hz), 3.69 (3H, s), 3.47 (1H, m), 2.73 (2H, t), 2.62 (1H, d, J = 6.4 Hz), 2.34 (1H, dd, J = 15.5 and 2.5 Hz), 1.90−1.40 (5H, m); *m/e* 304 (M^+ − CO), 276, 248. Anal. Calcd for $C_{14}H_{16}N_2O_4Fe$: C, 50.63; H, 4.86; N, 8.43. Found: C, 50.35; H, 4.66; N 8.16.

Tricarbonyl(7−10-*η*-1-oxo-9-methoxy-2-azaspiro[5.5]-undeca-7,9-diene)iron (7). To the amino complex **6** (460 mg) dissolved in methanol (50 mL) was added potassium carbonate (920 mg) and water (2 mL). The reaction mixture was refluxed under nitrogen for 2 days, after which most of the solvent was removed under reduced pressure. The crude product was

chromatographed on a silica gel column with chloroform:methanol (10:1) as eluent to give yellowish solid **7** in 75% yield (350 mg). Mp 211−213 °C. IR (KBr) ν_{max} 3195, 2041, 1968, 1662 cm^{-1}. ^{1}H NMR δ ($CDCl_3$) 5.09 (1H, dd, J = 6.7 and 2.5 Hz), 3.69 (3H, s), 3.46 (1H, m), 3.30 (2H, m), 2.60 (1H, d, J = 6.7 Hz), 2.23 (1H, dd, J = 14.6 and 2.5 Hz), 2.00−1.50 (4H, m), 1.41 (1H, dd, J = 14.6 and 2.5 Hz); *m/e* 333 (M^+), 305, 277, 249. HRMS Calcd for $C_{14}H_{15}NO_5Fe$: 333.0295. Found: 333.0300. Anal. Calcd for $C_{14}H_{15}NO_5Fe$: C, 50.48; H, 4.54; N, 4.20. Found: C, 50.28; H, 4.77; N, 4.44.

1−4-η-[5-Cyano-5-[3-methoxycarbonyl)propyl]-2-methoxycyclohexa-1,3-diene]tricarbonyliron (9). The addition of Me_3SiCN was caried out as described above. The cyanoester complex **9** was obtained in 70% yield. Mp 88−90 °C. IR (KBr) ν_{max} 2227, 2054, 1980, 1740 cm^{-1}. ^{1}H NMR δ ($CDCl_3$) 5.17 (1H, dd, J = 6.4 and 2.5 Hz), 3.70 (3H, s), 3.68 (3H, s), 3.47 (1H, m), 2.57 (1H, d, J = 6.4 Hz), 2.40 (3H, m), 1.90−1.60 (3H, m); *m/e* 361 (M^+), 333, 305, 277. Anal. Calcd for $C_{15}H_{15}NO_6Fe$: C, 49.89; 4.19; N, 3.88. Found: 49.76; H, 4.05; N, 3.83.

Tricarbonyl(7−10-η-3-oxo-9-methoxy-2-azaspiro[5.5]-undeca-7,9-diene)iron (10). The complex **9** (200 mg) was dissolved in ethanol (60 mL) and Raney nickel added, whereby it was reduced under hydrogen for 2 days. The catalyst was filtered and the solvent evaporated to dryness. The crude product was purified using preparative TLC (silica gel plate, 20 × 20 cm) with chloroform:methanol (20:1) as eluent to give pure product **10** as ivory-colored solid in 96% yield (177 mg). Mp 170−172 °C. IR (KBr) ν_{max} 2050, 1964, 1667 cm^{-1}. ^{1}H NMR δ ($CDCl_3$) 5.07 (1H, dd, J = 6.5 and 2.5 Hz), 3.66 (3H, s), 3.38 (1H, m), 3.09 (1H, d, J = 12.0 and 3.5 Hz), 2.66 (1H, J = 12.0 and 3.5 Hz), 2.40−2.10 (3H, m), 1.88, 1H, dd, J = 14.8 Hz and 2.5 Hz), 1.60−1.40 (3H. m); *m/e* 333 (M^+), 305, 277, 247. HRMS Calcd for $C_{14}H_{15}NO_5Fe$: 333.0295. Found: 333.0315. Anal. Calcd for $C_{14}H_{15}NO_5Fe$: C, 50.48; H, 4.54; N, 4.20. Found: C, 50.69; H, 4.62; N, 4.05.

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