ORGANOMETALLICS
Note

Organometallics **2010,** *29,* 3669–3671 3669
DOI: 10.1021/om100521s

Pyridyl-Cyclopentadiene $Re(CO)_2^+$ Complexes as a Compact Core System for SPECT Ligand Development

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Received May 27, 2010

Summary: An η^1,η^5-rhenium complex has been prepared, starting from a $CpRe(CO)_3$ complex substituted with a pendant aromatic amine. This unique complex has potential application as a surrogate for a technetium-99m complex, a common radioisotope for biomedical imaging applications. Chelation occurred via photochemical decarbonylation of the rhenium, which opened a binding site for the aromatic amine.

Introduction

Because of its long half-life (6 h) and widespread availability, $^{99\,m}$Tc is currently used for approximately 85% of all clinical radioisotopic imaging applications.[1,2] Examples of the use of technetium in imaging include simple complexes such as the myocardial imaging agent Sestamibi,[3,4] as well as technetium-containing complexes appended to biological molecules of interest,[5] often macromolecules.[6−8] A commonly used pendent complex is the organometallic cyclopentadienyl tricarbonyl technetium unit, $CpTc(CO)_3$, because of its high stability[9] and the ease with which it can be prepared.[10−12] The $CpTc(CO)_3$ unit works well with high molecular weight biomolecules, whose physical and chemical properties dominate over the relatively small pendant complex. With smaller biological molecules and small-molecule drugs, however, the polarity and steric size of the three carbonyl ligands have the potential to negatively affect pharmacokinetic properties. Burying the metal further within the ligand would reduce its accessibility to solvent and replace one of its CO groups, a change that is predicted to reduce its surface polarity by approximately one log unit.[13] With this goal in mind, it was decided to synthesize a model complex using rhenium in place of technetium, with a pyridylmethyl substituent added to the Cp core. The nitrogen of the pyridine should allow it to displace a CO under photochemical conditions and bind the metal with a second binding site, as shown in Figure 1.[14]

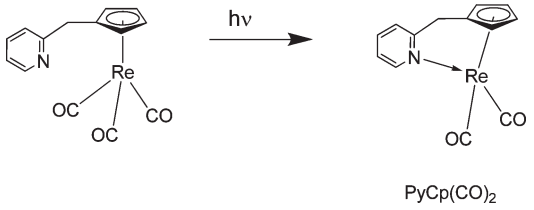

Figure 1. Photochemical cyclization.

Results

To reduce exposure to radioactive isotopes, all synthetic steps were performed using rhenium instead of technetium.[15] Rhenium has been widely used as a surrogate for technetium because rhenium analogues of technetium compounds can generally be prepared under similar conditions and their physical properties are similar. The synthesis of

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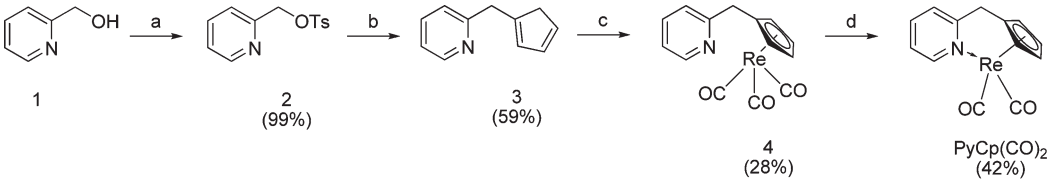
Published on Web 07/20/2010

Scheme 1. Synthesis of the Pyridyl-Cyclopentadienyl Core



(a) TsCl, KOH, THF, RT, overnight. (b) NaCp, THF, -78 °C. (c) n-BuLi, $[ReBr(THF)_2(CO)_3]_2$, RT, 20 min. (d) hn, 300 nm. 90 min.

η^1,η^5-pyridylmethylcyclopentadienyl rhenium(I) dicarbonyl, $PyCp(CO)_2$, involves two key steps: the attachment of the metal tricarbonyl to a cyclopentadienide, and the displacement of one carbonyl ligand and the concomitant cyclization to produce an η^1,η^5 complex. Production of the pyridyl cyclopentadiene **3** proceeds in two steps from commercially available 2-pyridylmethanol (**1**), as shown in Scheme 1. α-Hydroxypicoline (**1**) was activated as the tosylate **2**,[16] which was displaced using Cp anion to form the monosubstituted cyclopentadiene **3**. Cyclopentadiene **3** was isolated as a mixture of isomers, due to the propensity of cyclopentadienes to undergo a 1,5-hydride shift, which in the case of substituted rings results in double-bond regioisomers. No Diels−Alder dimerization of **3** was observed under standard isolation and characterization conditions at room temperature. Deprotonation of the cyclopentadiene **3** isomers formed one nucleophilic dienide, which coordinated to a rhenium tricarbonyl complex to form the piano-stool pyridylmethyl Cp complex **4**.[17] The essential pyridine to rhenium cyclization occurs via photoirradiation under inert atmosphere to provide the desired rhenium dicarbonyl complex **5**.[14]

Discussion

Several examples exist in the literature of transition metals, including rhenium, with bidentate *alkyl-amine*-substituted cyclopentadienide ligands.[14,18−20] Examples of Cp ligands with aromatic amine substituents are far less common[21,22] and are not uniformly bidentate.[23] To our knowledge, this is the first example of a pendant aromatic amine bound to rhenium. Our interest in such complexes is twofold: rhenium complexes serve as model systems for technetium in the development of imaging agents;[15] and there is a need to modify the *in vivo* stability and pharmacokinetic properties of certain metal complexes such that they make effective small-molecule imaging agents.

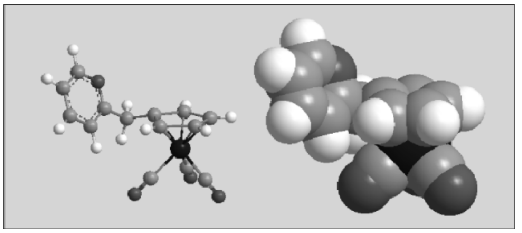


Figure 2. Space-filling model of the η^5-complex.

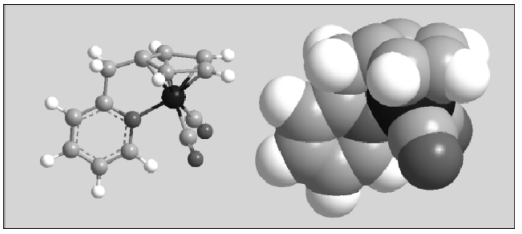


Figure 3. Space-filling model of the η^1,η^5-complex.

Comparison of the energy minimization space-filling models of the η^5-complex (Figure 2) and the η^1,η^5-complex (Figure 3) illustrates the change in topology that arises from pyridine chelation. The original $CpRe(CO)_3$ complex **4** (Figure 2) shows the classic "piano-stool" structure, with the η^5-tricarbonyl metal system extending normal to the plane of the cyclopentadienyl ring on one side, with the pyridine substituent angled to occupy space on the other side of the Cp ring. By contrast, in the η^1,η^5-complex **5** (Figure 3), the pyridyl ring, in replacing one of the CO ligands, has rotated downward onto the other face of the Cp ring, where it overall wraps itself much more around the metal center, making a more compact structure. We were surprised, however, to find that chelation did not have the effect on surface polarity predicted by calculations. Using an ethyl acetate/hexanes mixture showed no separation of the two complexes by thin-layer chromatography. Instead, purification of the η^1,η^5-complex was accomplished by precipitation from a mixture of both complexes. The addition of hexanes to a

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methylene chloride solution resulted in the selective precipitation of the η^1,η^5-complex, suggesting that the surface polarity was increased, rather than decreased as expected. It appears that the loss of a polar CO ligand was more than compensated for by the introduction of formal charge on the pyridyl nitrogen.

Conclusion

We present here the synthesis of an η^1,η^5-cyclopentadienide rhenium complex with an aromatic amine side chain chelated to the metal center. Polarity increased slightly due to chelation by the aromatic amine, a change that may be beneficial for some imaging applications. The selective synthesis of monosubstituted Cp rings for use as tethered imaging agents may be challenging; thus, the use of an appropriately substituted alkylpyridyl methanol would allow for introduction of a tether. Chelation could then be used, or not, depending on the requirements to adjust the polarity or steric contour of the system.

Experimental Section

General Comments. Synthetic operations were carried out under an atmosphere of nitrogen or argon, using standard Schlenk techniques, and flame-dried glassware was used. All reagents are commercially available from Aldrich, Strem, or Fisher and were used without further purification, unless otherwise stated. Solvents were purified using a solvent dispensing system fabricated by J. C. Meyer, based on a design published by Pangborn et al.[24]

Reaction progress was monitored using analytical thin-layer chromatography (TLC) on silica gel 60 F_{254} plastic plates from EM Science. Visualization was achieved by either using UV light (254 nm) or phosphomolybdic acid indicator. Purification was done either by recrystallization or by flash column chromatography using Woelm silica gel (0.040−0.063 mm).[25]

^{1}H and ^{13}C NMR spectra were recorded on a U400 or U500 Varian FT-NMR spectrometer. Chemical shifts (δ) are reported in parts per million downfield from tetramethylsilane or by reference to the proton resonance of incomplete deuteration of NMR solvent. Both high- and low-resolution electron impact (EI) and chemical ionization (CI) mass spectra were obtained on a VG Instruments 70-VSE spectrometer.

2-Pyridylmethyl Toluene-4-sulfonate (2). To a stirred suspension of crushed KOH (4.702 g, 83.37 mmol) in dry tetrahydrofuran (100 mL) were added 10 drops of deionized water and 2-pyridylcarbinol (**1**) (1.725, 15.81 mmol). Stirring was continued for 18 h at RT. The white solid was filtered and washed with diethyl ether, and the mother liquor was dried over Na_2SO_4. Solvent was removed to provide a red oil (4.128 g, 99%). The product was taken on without need for further purification. ^{1}H NMR ($CDCl_3$): δ 8.41 (ddd, 1H, J = 4.88, 4.39, 0.98), 7.73 (AA′XX′, 2H, J = 8.30), 7.58 (dd, 1H J = 7.81, 7.69), 7.29 (d, 1H, J = 7.81), 7.24 (AA′XX′, 2H, J = 8.55), 7.12 (ddd, 1H, J = 7.69, 4.80, 0.49), 5.05 (s, 2H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.28, 71.54, 121.69, 123.10, 127.67, 129.64, 132.33, 136.65, 144.82, 148.99, 163.22. EI-MS: m/z 264.0 (M^+). Anal. Calcd for $C_{13}H_{13}NO_3S$: 264.068748. Found: HREI-MS 264.069052.

2-Cyclopenta-1,4-dienylmethylpyridine (3). To a solution of 2.0 M sodium cyclopentadienide (150 mL, 300 mmol) was added a solution of 2-pyridylmethyl toluene-4-sulfonate (**2**) (4.090 g, 15.53 mmol) at 0 °C in tetrahydrofuran (100 mL). Stirring was continued for 90 min. The solution was then quenched with 5 mL of 6 N HCl, neutralized with $NaHCO_3$, and filtered through Celite. The solvent was removed, and the residue was redissolved in ethyl acetate. The organic phase was washed with saturated NaCl, filtered through Celite, and dried over Na_2SO_4. Solvent was removed to provide a brown oil, which was was purified to a mixture of isomers by column chromatography over triethylamine-treated silica gel, eluted with 50% ethyl acetate/hexanes (brown oil, 1.435 g, 59%). ^{1}H NMR ($CDCl_3$): δ 8.52 (m, 0.99H), 7.56 (m, 1.07H), 7.14 (m, 1.07H), 7.09 (m, 1.08H), 6.41 (m, 1.75H), 6.24 (m, 1H), 6.07 (m, 0.63H), 3.90 (m, 2.2H), 2.97 (m, 1.31H), 2.89 (m, 1.18H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.98, 39.90, 41.28, 43.15, 121.07, 122.86, 122.90, 128.19, 128.57, 131.69, 132.25, 134.07, 134.27, 136.33, 136.39, 144.06, 146.31, 149.17, 149.21, 160.14, 160.60. EI-MS: m/z 157.1 (M^+). Anal. Calcd for $C_{11}H_{11}N$: 156.081324. Found: HREI-MS 156.081071.

η^5-Cyclopentadienylmethylpyridinylrhenium Tricarbonyl (4). To a solution of cyclopentadienylmethylpyridine (**3**) (0.222 g, 1.41 mmol) at −78 °C in tetrahydrofuran (10 mL) was added 2.0 M n-BuLi (1.4 mL, 2.8 mmol). The solution was stirred for 5 min. A solution of $[ReBr(THF)(CO)_3]_2$ (0.603 g 0.71 mmol) in tetrahydrofuran (10 mL) was cannulated into the solution and stirring continued for 20 min, followed by quenching with 3 mL of methanol and 2 mL of 1 N HCl. The aqueous phase was extracted with methylene chloride. The organic extracts were washed with saturated NaCl and dried over Na_2SO_4. Solvent was removed to provide a brown oil, which was purified by column chromatography over triethylamine-treated silica gel, eluted with 50% ethyl acetate/hexanes (brown oil, 0.171 g, 28%). ^{1}H NMR ($CDCl_3$): δ 8.53 (dd, 1H, J = 4.88, 0.90), 7.63 (ddd, 1H, J = 7.81, 7.57, 1.79), 7.18 (d, 1H, J = 7.81), 7.15 (dd, 1H, J = 7.57, 0.98), 5.37 (t, 2H, J = 2.20), 5.21 (t, 2H, J = 2.20), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.77, 83.47, 84.73, 107.18, 121.90, 122.75, 136.85, 149.31, 158.97, 194.19. CI-MS: m/z 428.0 ($M^+ + 1$). Anal. Calcd for $C_{14}H_{11}NO_3Re$: 428.029658. Found: HRCI-MS 428.02965.

η^1,η^5-Pyridylmethylcyclopentadienylrhenium Dicarbonyl ($PyCp(CO)_2$). A solution of cyclopentadienylrhenium (**4**) (0.171 g 0.40 mmol) in dry tetrahydrofuran (10 mL) in a quartz Schlenk tube under a nitrogen atmosphere was irradiated in a Rayonet apparatus under a nitrogen atmosphere with 300 nm low-pressure Hg lamps for 90 min. Solvent was removed to provide a red-brown solid, which was purified by precipitation from methylene chloride using hexanes (red solid, 0.068 g, 42%). ^{1}H NMR ($CDCl_3$): δ 8.94 (dd, 1H, J = 4.89, 1.52), 7.39 (ddd, 1H, J = 7.81, 7.57, 1.54), 6.80 (dd, 1H, J = 5.13, 0.73), 6.78 (dd, 1H, J = 4.88, 0.73), 5.47 (t, 2H, J = 2.08), 5.07 (t, 2H, J = 2.08), 3.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.75, 77.19, 80.20, 122.89, 123.45, 134.78, 159.68, 176.23, 204.69. FAB-MS: m/z 399.1 (M^+). Anal. Calcd for $C_{13}H_{10}NO_2Re$: 397.02415. Found: HRFAB-MS 397.0240.

Acknowledgment. We thank the United States Army Medical Research and Materiel Command Breast Cancer Research Program DAMD-17-03-1-0681 and the National Institutes of Health PHS 5R01 CA025836 for funding.

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