A 2-Azafulvenium and 3-Vinylpyrrole Complex of Osmium(II) from an η^2-Pyrrole and Its Efficient Conversion into a Highly Substituted Indole

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Received April 27, 1994

The indole nucleus, found in numerous classes of alkaloids and alkaloid derivatives, is usually synthesized by an intramolecular ring closure of a monsubstituted or an *ortho*-disubstituted benzene precursor.[1,2] Far less common are approaches which assemble the six-membered ring starting with a substituted pyrrole.[3] Herein, we wish to report a convenient synthesis of a 3-vinylpyrrole complex of osmium(II), readily prepared by an aldol condensation of acetone with a 4,5-η^2-pyrrole precursor, which readily undergoes a stereoselective Diels–Alder reaction to give a highly functionalized tetrahydroindole nucleus.

The pentaammineosmium(II) complex of 1-methylpyrrole (**1**) is readily prepared from the pyrrole and $Os(NH_3)_5(OTf)_3$ in virtually quantitative yield (90–95%).[4] Relative to the uncomplexed heterocycle, the complex $[Os(NH_3)_5(4,5\text{-}\eta^2\text{-}1\text{-methylpyrrole})]^{2+}$ (**1**) shows enhanced electrophilic reactivity at C(3).[5] Thus, treatment of **1** (0.10 mmol) with 1 equiv of *tert*-butyldimethylsilyl triflate (TBSOTf) in the presence of excess acetone (~2 equiv in CH_3CN) produces a TBS-substituted aldol product, **2** (Figure 1).[6] Characterized in CD_3CN solution, this product has ^1H and ^{13}C NMR signals corresponding to a 3*H*-pyrrolium complex of pentaammineosmium(II)[5] and two diastereotopic methyl groups. The reaction of **2** with the base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) catalyzes an elimination of TBSOH, and the subsequent deprotonation of the azafulvenium intermediate, **3**[7] (*vide infra*), gives the complex $[Os(NH_3)_5(4,5\text{-}\eta^2\text{-}1\text{-methyl-3-(2-propenyl)pyrrole})]^{2+}$ **4** in an overall yield of 86% from the free pyrrole.[8] In addition to spectroscopic features consistent with other 3-substituted pyrrole complexes of Os(II), the β-vinylpyrrole complex **4** is characterized by two broadened singlets in the ^1H NMR at 5.25 and 4.45 ppm (acetone-d_6) and a ^{13}C NMR signal at 104.5 ppm corresponding to the diastereotopic methylene group. A cyclic voltammagram of **4** (100 mV/s, TBAH/CH_3CN) shows a pseudoreversible Os(III/II) reduction potential with $E_{1/2}$ = +0.26 V (NHE), confirming that the metal remains bound to the pyrrole ring (*vide infra*).[9]

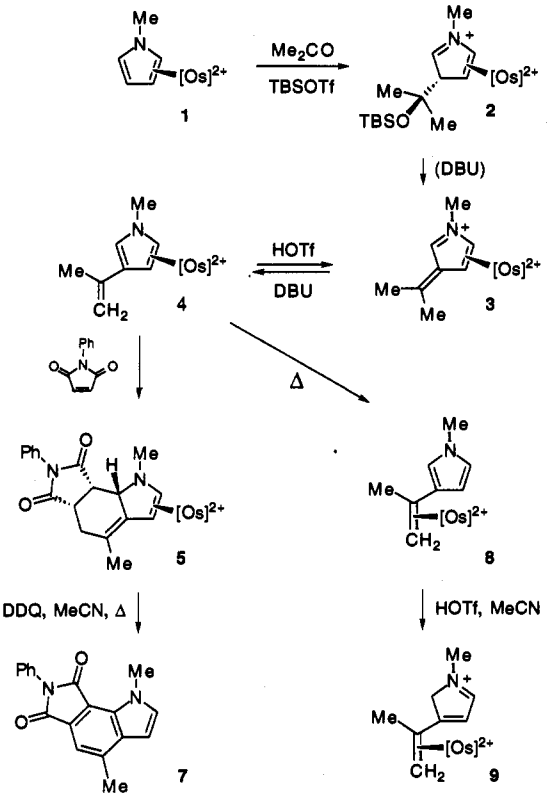

Figure 1. Synthesis and reactivity of the β-vinylpyrrole complex **4**. $[Os]^{2+}$, $[Os^{II}(NH_3)_5]^{2+}$; all osmium compounds are isolated as triflate salts.

Protonation of the β-vinylpyrrole complex **4** (HOTf, MeOH) cleanly regenerates the intermediate **3**,[10] a 3,4-η^2-2-azafulvenium complex of osmium(II). This novel species, which is stable for several hours at 80 °C in CD_3CN or D_2O solution, has a low-energy charge transfer band at 592 nm (CH_3CN, ϵ = 750 (M^{-1} cm^{-1}) that is responsible for its turquoise appearance and an irreversible oxidation wave at $E_{p,a}$ = +1.22 V. In addition, the azafulvenium salt, **3**, shows an iminium ^{13}C resonance for C(2) that is ~15 ppm upfield from that of more typical 3*H*-pyrrolium complexes[11] and is indicative of extended conjugation.[12]

The uncoordinated portion of the β-vinylpyrrole complex **4** approximates an electron-rich diene and, as such, readily undergoes a Diels–Alder cycloaddition with suitable electron-deficient dienophiles. For example, the reaction of **4** with 1 equiv of *N*-phenylmaleimide (CH_3CN, 15 min) gives a single isomer of the substituted 5,6,7,7a-tetrahydroindole complex **5** in 80% isolated yield and >95% de. NOE studies confirm that this product is the result of an *endo* cycloaddition where the dienophile attacks the ring face opposite that of metal coordination (Figure

(1) Couture, A.; Deniau, E.; Gimbert, Y.; Grandclaudon, P. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2463 and references therein.

(2) For a review on indole syntheses involving Pd, see: Hegedus, L. S. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1113.

(3) For examples of Diels–Alder reactions with vinyl pyrroles, see: Jones, R. A.; Saliente, T. A.; Arques, J. S. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2541 and references therein. For a recent synthesis of 3-vinylpyrrole, see: Settambolo, R.; Lazzaroni, R.; Messeri, T.; Mazzetti, M.; Salvadori, P. *J. Org. Chem.* **1993**, *58*, 7899.

(4) Synthesized by Mg^0 reduction of $Os(NH_3)_5(OTf)_3$ in the presence of excess 1-methylpyrrole (ca. 8–10 equiv) in DMAc solution (see ref 5). In order to use the standard nomenclature for the uncoordinated ligand, the osmium is coordinated at C(4)–C(5) by definition. All osmium compounds are handled as their triflate salts.

(5) Hodges, L. M.; Gonzalez, J.; Koontz, J. I.; Myers, W. H.; Harman, W. D. *J. Org. Chem.* **1993**, *58*, 4788 and references therein.

(6) All reactions were carried out under a nitrogen atmosphere in a Vacuum Atmospheres glovebox unless otherwise noted. Compounds **3–5**, **7**, and **8** have been analyzed by elemental analysis for C, H, and N and all show agreement within 0.4% of calculated values. ^1H NMR data for **2** (300 MHz, CD_3CN): δ 8.71 (s, 1H), 6.30 (d, J = 4.5 Hz, 1H), 4.69 (d, J = 4.5 Hz, 1H), 4.50 (br s, 3H), 3.82 (s, 3H), 3.27 (br s, 12H), 2.76 (s, 1H), 1.57 (s, 3H), 1.44 (s, 3H), 0.87 (s, 9H), 0.15 (s, 6H). ^{13}C NMR data for **2** (75 MHz, CD_3CN): δ 174.66 (CH), 75.15 (C, CH (overlap)), 67.88 (CH), 47.04 (CH), 42.58 (CH_3), 30.03 (CH_3), 28.26 (CH_3), 26.09 (CH_3)$_3$, 18.50 (C), –2.04 (CH_3)$_2$. The quartet for $CF_3SO_3^-$ (triflate) at 121 ppm (J = 318 Hz) is observed in the ^{13}C spectrum for all complexes but is not reported. The stucture of **2** is further supported by HETCOR data.

(7) While **3** cannot be isolated in this step, it can be cleanly regenerated by protonation of **4**.

(8) Overall yield of **4** from **1**: 91%. ^1H NMR data for **4** (acetone-d_6): δ 6.67 (s, 1H), 6.54 (d, J = 4.2 Hz, 1H), 5.74 (d, J = 4.2 Hz, 1H), 5.25 (s, 1H), 4.51 (br s, 3H), 4.45 (s, 1H), 3.59 (s, 3H), 3.49 (br s, 12H), 1.88 (s, 3H). ^{13}C NMR data for **4** (acetone-d_6): δ 140.94 (C), 126.33 (CH), 123.84 (C), 104.47 (CH_2), 80.27 (CH), 52.90 (CH), 37.67 (NCH_3), 20.74 (CH_3).

(9) Upon continued scanning, this oxidation gives rise to a new reversible couple at $E_{1/2}$ = +0.48 V corresponding to the linkage isomer **8**.

(10) ^1H NMR data for **3** (acetone-d_6): δ 9.10 (s, 1H), 7.14 (d, J = 4.2 Hz, 1H), 6.22 (d, J = 4.2 Hz, 1H), 5.19 (br s, 3H), 4.10 (s, 3H), 3.97 (br s, 12H), 2.08 (s, 3H), 1.94 (s, 3H). ^{13}C NMR data for **3** (acetone-d_6): δ 160.44 (C), 156.20 (CH), 141.64 (C), 73.77 (CH), 42.04, 40.29 (CH, NCH_3), 25.15 (CH_3), 24.15 (CH_3).

(11) The C(5)–H signal shifts from 6.76 to 7.14 ppm, and the C(4)–H signal shifts from 5.11 to 6.22 ppm (acetone-d_6) compared to those of the 4,5-η^2-$[Os(NH_3)_5]$-1-methyl-3*H*-pyrrolium complex; the C(2) pyrrolium carbon signal shifts from 173.99 to 156.20 ppm.

(12) Breitmaier, E.; Voelter, W. In *Carbon-13 NMR Spectroscopy*, 3rd ed.; VCH Publishers: New York, 1987; p 114.

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1).[13,14] Treatment of cycloadduct **5** with 2.0 equiv of DDQ (CH_3CN) followed by heating (1 h, 120 °C) decomplexes and oxidizes the organic ligand to yield the substituted indole **7** in 69% isolated yield.[15,16]

At 20 °C, in solution or in the solid state, the β-vinylpyrrole complex **4** undergoes a linkage isomerization (CD_3CN, $t_{1/2} \sim 36$ h) to generate compound **8** (Figure 1), where the metal has moved from the heterocycle to the vinyl substituent.[17] ^1H NMR data for **8** show three pyrrole resonances ranging from 5.7 to 6.6 ppm and two vinyl signals (3.78, 3.23 ppm) that are shifted considerably upfield relative to those of the precursor **4**. A cyclic voltammogram of **8** shows a reversible oxidation wave at +0.48 V, significantly positive of the ring-bound precursor **4**.[18]

Given the dramatic increase in the basicity ($\sim 10^{10}$) of the pyrrole ring upon complexation to osmium(II),[19] we questioned if the metal could still influence the reactivity of the aromatic heterocycle when bound to a vinyl substituent in conjugation with the ring. Protonation of **8** (HOTf, CH_3CN) occurs exclusively at C(2) to give the 2*H*-pyrrolium adduct **9**.[20] The structure of **9** is supported by ^1H and ^{13}C NMR as well as NOE data. Despite its dipositive charge, compound **8** is found to be approximately 30 times *more* basic than 1-methylpyrrole (for **9**, $pK_a = -1.5$).[21] This observed increase in basicity, together with the high regioselectivity of protonation, indicates that the metal still modestly influences the reactivity of the aromatic ring through back-bonding, even though it is not directly coordinated to the ring. In contrast to the conjugate acid of 1-methylpyrrole,[22] **9** shows no detectable decomposition in acetonitrile over several days.[23]

In related work, 3-vinylpyrrole complexes of osmium(II) have also been prepared from **1** by conjugate addition of an alkyne or by an acetylation/methylation/deprotonation sequence. Given that the cycloaddition reaction may also be carried out with a variety of dienophiles, the method described herein appears to offer exceptional flexibility in the preparation of highly-substituted indoles.[24] The full scope of these reactions is currently under investigation.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society (PRF No. 26027-AC), the Camille and Henry Dreyfus Foundation, the National Institutes of Health (R01 GM49236-01A1), and the National Science Foundation (NYI program) for their generous support of this work. We also wish to thank Dr. Laurie Kelsh for assistance in obtaining 500 MHz 2D ^1H NMR spectra required for the determination of stereochemistry for **5**.

Supplementary Material Available: Additional information on the synthesis and characterization of compounds **1–9** (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(13) The preparation of **5** can be performed using a one-pot procedure starting from **1**. Structure determined by ^1H and ^{13}C NMR along with DEPT and HETCOR data. ^1H NMR data for **5** (DMSO-d_6): δ 7.46 (t, 2H), 7.41 (t, 1H), 7.07 (d, 2H, Ph), 5.51 (d, J = 4.2 Hz, 1H), 4.19 (br s, 3H), 3.98 (d, J = 4.2 Hz, 1H), 3.49 (t, J = 8.1 Hz, 1H), 3.31 (br s, 12H), 3.11 (dd, J = 6.0, 5.1 Hz, 1H), 2.85 (d, 1H), 2.82 (s, 3H), 2.43 (d, J = 13.8 Hz, 1H), 2.02 (dd, J = 14.4, 4.8 Hz, 1H), 1.87 (s, 3H). ^{13}C NMR data for **5** (DMSO-d_6): δ 178.34 (C), 174.83 (C), 142.53 (C), 132.63 (C), 128.82 (CH), 128.07 (CH), 126.67 (CH), 119.89 (C), 81.65 (CH), 62.40 (CH), 42.77 (CH), 38.51 (CH), 36.67 (CH), 35.54 (CH_3), 30.24 (CH_2), 20.64 (CH_3).

(14) Stereochemistry and proton assignments were determined by 500 MHz NOESY and COSY data, which are consistent with an *endo* cycloadduct with addition coming from the ring face opposite metal coordination: the *cis*-NH_3 protons show an NOE with C(7a)–H. *Endo* stereochemistry is consistent with NOESY data of the ring protons (C5–C7a): C(7a)–H shows an NOE with C(7)–H as well as one of the C(5) protons; C(7)–H shows an NOE with C(7a)–H, C(6)–H, and both C(5) protons.

(15) Oxidation of **5** with 1.0 equiv of DDQ in the presence of excess HOTf gives 17% isolated yield of the 6,7-dihydroindole derivative (**6**) upon workup. See supplementary material for experimental details and characterization data for **6**.

(16) ^1H NMR data for **7** (500 MHz, $CDCl_3$): δ 7.51 (t, 2H), 7.50 (s, 1H), 7.46 (d, 2H), 7.39 (t, 1H), 7.23 (d, J = 3.0 Hz, 1H), 6.65 (d, J = 3.0 Hz, 1H), 4.30 (s, 3H), 2.66 (s, 3H). ^{13}C NMR data for **7** (125 MHz, $CDCl_3$): δ 168.70 (CO), 167.63 (CO), 137.83 (C), 135.42 (C), 133.94 (CH), 132.16 (C), 131.09 (C), 128.92 (CH), 127.60 (CH), 127.27 (C), 126.76 (CH), 114.52 (CH), 112.82 (C), 101.85 (CH), 37.69 (NCH_3), 19.26 (CH_3).

(17) The reaction is complete in ca. 30 min at 70–80 °C using a cosolvent mixture of DME/DMAc. ^1H NMR data for **8** (CD_3CN): δ 6.53 (m, 1H), 6.48 (m, 1H), 5.74 (m, 1H), 4.06 (br s, 3H), 3.78 (br s, 1H), 3.57 (s, 3H), 3.23 (br s, 1H), 2.89 (br s, 12H), 1.41 (s, 3H). ^{13}C NMR data for **8** (CD_3CN): δ 131.24 (C), 123.68 (CH), 118.71 (CH), 105.45 (CH), 52.05 (C), 43.55 (CH_2), 36.46 (NCH_3), 24.50 (CH_3).

(18) Electrochemical experiments show that when the ring-bound β-vinylpyrrole complex (e.g., **4**) is oxidized by one electron ($E_{p,a}$ = +0.26 V), linkage isomerization on Os(III) occurs rapidly ($t_{1/2} \approx 1$ s) to give the vinyl-bound Os(III) complex. Being a better oxidant than its precursor, this compound accepts an electron from remaining starting material to generate **8**, which can then be reoxidized at +0.48 V.

(19) The pK_a of the β-protonated 1-methylpyrrole complex (ring bound) is +5.6; the pK_a of the corresponding α-protonated tautomer is +7.8. See: Myers, W. H.; Koontz, J. I.; Harman, W. D. *J. Am. Chem. Soc.* **1992**, *114*, 5684.

(20) ^1H NMR data for **9** (CD_3CN): δ 8.48 (s, 1H), 6.32 (d, J = 0.9 Hz, 1H), 4.64 (d, J = 2.4 Hz, 1H), 4.54 (br s, 3H), 4.28 (d, J = 1.8 Hz, 1H), 4.2–4.5 (m, 2H), 3.58 (s, 3H), 3.30 (br s, 12H), 1.41 (s, 3H). ^{13}C NMR data for **9** (CD_3CN): δ 187.69 (C), 171.14 (CH), 116.55 (CH), 68.32 (CH_2), 49.13 (CH_2), 47.89 (C), 39.76 (NCH_3), 22.85 (CH_3).

(21) The pK_a of **9** was established through measurement of its equilibrium with an excess of 1-methylpyrrole ($pK_a = -2.9$) in CD_3CN solvent. Chadwick, D. J. In *Pyrroles Part One: The Synthesis and the Physical and Chemical Aspects of the Pyrrole Ring, v. 48*; Jones, R. A., Ed.; John Wiley & Sons: New York, 1990.

(22) Protonated 1-methylpyrrole reacts with acetonitrile to give an α-iminium-substituted pyrrole.

(23) Attempts to reduce **9** (Bu_4NBH_3CN) have resulted in deprotonation. Repeated attempts to carry out electrophilic additions to **8** using methyl triflate, Ac_2O/DMAP, methyl acrylate/TBSOTf, methyl vinyl ketone/TBSOTf, and methylacetonitrilium triflate have resulted in either the recovery of starting material or mixtures of products.

(24) β-Vinylpyrrole complexes have been prepared with alkyl, acetyl, and methoxy substitutents on the vinyl group, and these complexes also undergo cycloaddition with maleimides. The β-vinylpyrrole complex **4** reacts with the less activated dieneophiles such as dimethyl fumarate and methyl vinyl ketone to produce similiar tetrahydroindole adducts.