Preparation of a Rhena-β-ketoimine Ester Derivative of Methylfluorophosphonic Acid: a Potential Heavy-atom Labeling Reagent for Hydroxyl Groups

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In previous work, we have prepared rhena-β-ketoimine derivatives of several amino acid esters and biologically-important molecules containing 2-ethylamino groups [1–3]. These molecules are labeled with a rhenium organometallic moiety via a Schiff-base condensation between a rhena-β-diketone and a primary amino group on the substrate molecule. The resulting rhena-β-ketoimine products represent rhenium-labeled compounds having good chemical stability and a strong covalent link between the rhenium moiety and the substrate molecule. Furthermore, because of the apparent similarity of Re and Tc organometallic chemistry, the possibility of preparing radiolabeled derivatives by a similar method also exists.

To overcome the limitations of choice of solvent and the strong basicity of the primary amine in the above mentioned Schiff-base reactions, we devised a new strategy for preparing rhenium-labeled molecules. In this approach, rhena-β-ketoimine moieties are attached to reagent molecules that are known to react with specific functional groups of substrate molecules, such as sulfhydryl and amino groups [4]. We now report the successful preparation of a rhena-β-ketoimine ester derivative of methylfluorophosphonic acid. Methylfluorophosphonic acid esters have been used as effective and specific reagents for connecting alcoholic residues [5–7]. Condensation of this rhenium-labeled reagent with ethanol is reported as a model reaction.

Experimental

All reactions were performed under dry, prepurified nitrogen at 25 °C unless states otherwise. Diethyl ether, THF, and hexane were dried over Na–K alloy with added benzophenone, and methylene chloride was dried over P_2O_5. Ethanolamine was vacuum distilled prior to use. Infrared spectra were recorded on a Perkin-Elmer 727 spectrometer as solutions in 0.10 mm sodium chloride cavity cells using the solvent as a reference and a polystyrene film as a calibration standard. Proton NMR spectra were obtained on a JEOL MH-100 NMR spectrometer using Me_4Si as an internal reference. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. The complex, *cis*-$(OC)_4Re(CH_3CO)_2H$ (**1**) was prepared by a literature method [8]. Methylphosphonic difluoride and ethanolamine were obtained commercially.

cis-(OC)$_4$Re[CH$_3$C(O)][CH$_3$CN(CH$_2$CH$_2$OH)(H)] (2)

To a solution of 0.50–0.75 g of **1** in 10 ml of CH_2Cl_2 was added 1 mol equivalent of ethanolamine. The yellow reaction solution turned to pale lemon yellow within 30 s. The solution was stirred for 24 h, and then the solvent was removed at reduced pressure. The reaction residue was taken up in CH_2Cl_2 (2 ml) and was chromatographed on Florisil with CH_2Cl_2. The solvent was removed *in vacuo*, yielding **2** as a viscous golden oil (yield 61%); IR (CH_2Cl_2) 2080(w), 1990(vs), 1975(sh), 1948(s), 1560(br,m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.61(s, 3, CH_3), 2.73(s, 3, CH_3), 3.36(s, 1, OH), 3.69(t, 2, CH_2, J_{HH} = 6 Hz), 4.08 (t, 2, CH_2, J_{HH} = 6 Hz), 13.02(s, br, 1, iminium H). *Anal.* Calc. for $C_{10}H_{12}NO_6Re$ C, 28.04; H, 2.82; N, 3.27. Found: C, 28.09; H, 3.08; N, 3.05%.

cis-(OC)$_4$Re[CH$_3$C(O)]{CH$_3$CN[CH$_2$CH$_2$OP(O)(F)-CH$_3$](H)} (3)

To a solution of 0.50–1.50 g of **2** in 10 ml of CH_2Cl_2 was added 1 mol equivalent of triethylamine, followed by addition of 1 mol equivalent of $(CH_3P(O)F_2$. The mixture was stirred for 4 h, after which time the solvent was removed *in vacuo*. The residue was taken up in 1 ml of CH_2Cl_2 and was chromatographed on Florisil with CH_2Cl_2. Removal of the solvent *in vacuo* gave **3** as a viscous yellow oil (yield 43%): IR (CH_2Cl_2) 2055(w) 2000(sh), 1975(vs) 1940(m), 1600(w) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.78(d of d, 3, CH_3 J_{PH} = 20 Hz J_{FH} = 6 Hz), 2.62 (s, 3, CH_3), 2.76 (s, 3, CH_3), 3.89 (m, 2, CH_2) 4.57 (m, 2, CH_2), 13.43 (s, br, 1, iminium H). *Anal.* Calc. for $C_{11}H_{14}NO_7PF \cdot 0.5H_2O$: C, 25.53; H, 2.91. Found: C, 25.52; H, 3.00%

cis-(OC)$_4$Re[CH$_3$C(O)]{CH$_3$CN[CH$_2$CH$_2$OP(O)-(CH$_3$)OCH$_2$CH$_3$][(H)} (4)

To a solution of 0.08–0.10 g of **3** in 5 ml of CH_2Cl_2 was added 1 mol equivalent of triethylamine, followed by addition of 1 mol equivalent of ethanol. The mixture was stirred for 24 h, after which time the solvent was removed *in vacuo*. The residue was taken up in 1 ml of CH_2Cl_2, and was chromato-

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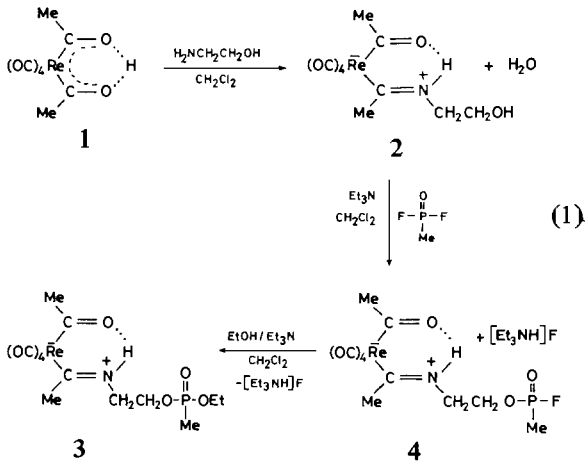
graphed on a short Florisil column with CH_2Cl_2. Removal of the solvent *in vacuo* yielded **4** as a light-yellow oil (yield 46%): IR(CH_2Cl_2) 2075(w), 1982(vs), 1960(vs), 1890(s), 1600 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.35 (t, 3, CH_3, J_{HH} = 7 Hz), 1.58 (d, 3, CH_3, J_{PH} = 19 Hz), 2.62 (s, 3, CH_3), 2.76 (s, 3, CH_3), 3.64 (m, 2, CH_2), 4.64 (m, 2, CH_2), 4.38 (m, 2, CH_2), 13.36 (s, br, 1 iminium H). *Anal.* Calc. for $C_{13}H_{19}NO_8PRe \cdot H_2O$: C, 28.26, H, 3.83; H, 2.53. Found: C, 28.06; H, 3.10; N, 2.26%.

Results and Discussion

The experimental results are summarized in eqn. (1). When the rhenaacetylacetone complex **1** is treated with ethanolamine, Schiff-base condensation occurs to give the rhena-β-ketomine complex **2**. Complex **2** contains an appended 2-ethanol substituent on the iminium nitrogen atom. This hydroxyl group condenses with methylphosphonic difluoride to give **3** as a rhena-β-ketoimine derivative of a methylfluorophosphonic acid ester. Complex **3** represents the target molecule where an organometallic moiety containing a heavy-metal atom is attached to the methylfluorophosphonate fragment (which is known to react specifically with hydroxyl groups on substrate molecules [5–7]). To demonstrate the feasibility of such labeling reactions, complex **3** condenses with ethanol to give **4** in 46% yield.



Complexes **2**–**4** are isolated as pure yellow oils. All three compounds exhibit the expected terminal carbonyl stretching bands in the infrared spectrum [1–3]. In addition, each complex exists predominantly as the intraisomer of the rhena-β-ketoimine moiety as indicated by the appearance of the iminium proton resonances at δ 13.02(**2**), δ 13.43(**3**) and δ 13.36(**4**) [1–3]. Complex **2** has a free hydroxyl proton resonance at δ 3.36. The ^1H NMR spectrum of **3** does not reveal a free hydroxyl group, as expected, and indicates the presence of a methylfluorophosphonate group. The methyl resonance of this moiety appears as a doublet of doublets showing both P–H (20 Hz) and F–H (6 Hz) coupling. In the spectrum of complex **4**, the phosphonic methyl resonance appears as a doublet showing only P–H coupling of 19 Hz.

We believe that compound **3** might be potentially useful as a heavy-atom labeling reagent for biologically-important molecules containing hydroxyl substituents.

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