Functionalized Rhenium(V) Organoimido Complexes as Potential Radiopharmaceuticals. 2. Synthesis, Structural Characterization, and Reactivity of *N*-Succinimidyl Ester Derivatives with Amines

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Received November 24, 1999

Organoimidorhenium(V) complexes were synthesized as potential labeling agents for biologically relevant organic amines using the preconjugate approach. The bistriphenylphosphine organoimidorhenium *N*-succinimidyl ester complex $Cl_3(PPh_3)_2Re{=}N\text{-}C_6H_4CO_2N\text{-}(COCH_2)_2$ (**2**) was synthesized and characterized by single-crystal X-ray analysis. Complex **2** was coupled in aqueous dimethylformamide solvent with a series of primary and secondary amines, amino acids, and a biotin−ethylenediamine derivative to give the corresponding amide complexes in good yields. These results demonstrate that the organoimido linkage is resistant toward hydrolysis and stable in the presence of more basic alkylamines. An unusual oxygen atom transfer reaction was observed between the byproduct *N*-hydroxysuccinimide and triphenylphosphine ligands when dichloromethane was used as solvent. The dithiocarbamate complexes $Cl[Et_2NCS_2]_2Re{=}N\text{-}C_6H_4CO_2N(COCH_2)_2$ (**3**) and $O[(Et_2NCS_2)_2Re{=}N\text{-}C_6H_4\text{-}CO_2N(COCH_2)_2]_2$ (**4**) were also synthesized from **2**. These complexes were unaffected by *N*-hydroxysuccinimide, but were not suitable for labeling due to hydrolysis of the organoimido groups under the reaction conditions.

Introduction

Biomolecules labeled with organometallic and coordination complexes have been developed for use as electron-transfer mediators, as probes for the active sites of enzymes, and for protein structural resolution with X-ray diffraction and electron microscopy.[1] The synthesis of radiopharmaceuticals represents another area where new technologies are necessary to overcome the challenges associated with labeling biomolecules with radioactive metals.[2] Peptides, antibodies, and steroids are all potential substrates for labeling with radioactive metals such as Tc-99m and Re-186/188 for diagnostic imaging and targeted radiotherapy, respectively. The ideal radiopharmaceutical would be easy to synthesize, exhibit stability and selective biodistribution *in vivo*, and then clear the body after the clinical procedure. These stringent requirements can ultimately be attained through multifaceted approaches leading to a diverse variety of candidate complexes for clinical trials.

Three general methods for producing metal bioconjugates are available: (1) direct labeling of biomolecules that contain a natural ligating or reactive group such as thiols; (2) the postconjugate approach where the biomolecule is first attached to a modified ligand that is then complexed with the metal; and (3) the preconjugate approach, where a metal complex is formed first and then attached to the biomolecule as an intact unit. With direct labeling it is difficult to control the site of attachment, the structure of the biomolecule can be disrupted, and redox changes at the metal can occur. The postconjugate approach provides a controlled ligand environment, but remains subject to problems during

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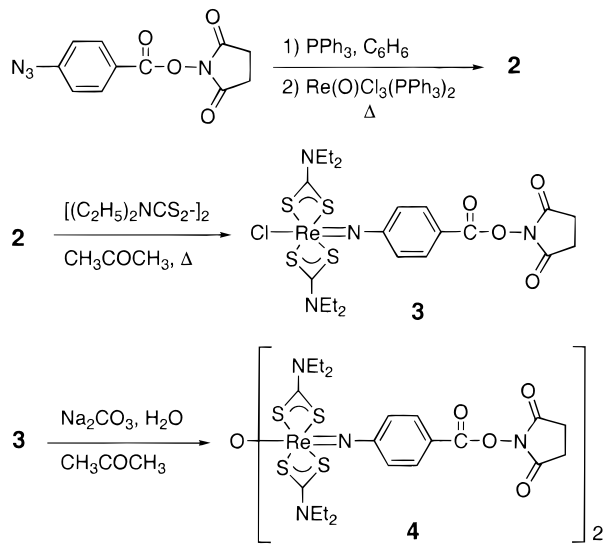
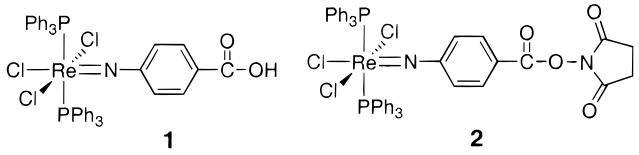
10.1021/om990929w CCC: $19.00
Publication on Web 03/31/2000

complex formation. The preconjugate approach offers greater control through the use of a purified metal complex, which only undergoes labeling with appropriately matched functional groups on the biomolecule. Amine side chain groups are commonly found on the biomolecules of interest and offer convenient sites for conjugation to a modified ligand system, due to the ease of formation of amide bonds with various activated carboxyl derivatives. Activated esters have been used to attach chelating ligands,[3] metal complexes,[4] and groups such as hydrazinopyridine to biomolecules.[5] The *N*-succinimidyl ester group is a convenient activating group for the acylation of amines and has been employed in the preconjugate approach to incorporate a variety of different classes of metal complexes,[6] including rhenium and technetium.[7]

We have investigated the suitability of the multiple bonding imido ligand for Tc and Re and recently reported the synthesis of aryl organoimido Re(V) complexes containing remotely functionalized carboxylic acid groups **1**.[8] These compounds are stable to air as solids and in solution, and Re-188 complexes can be synthesized at tracer levels and purified by HPLC chromatography using aqueous acetonitrile eluent. The multiply bonded organoimido group provides a direct covalent linkage between the organic and metal components. With this mode of attachment it is possible to fine-tune desirable properties of size, charge, and lipophilicity by varying labile ligands in the coordination sphere, an option unavailable to chelates. Therefore we have considered the development of organoimido complexes that are remotely functionalized with active ester analogues which would be suitable for labeling amines by the preconjugate approach. This approach requires that the organoimido linkage be resistant to hydrolysis under aqueous conditions and exhibit stability in the presence of alkylamines, which are both stronger bases and potential ligands. We describe here the synthesis and X-ray stucture of the activated organoimido *N*-succinimidyl ester **2** and dithiocarbamate derivatives **3** and **4**, and an investigation of their reactivity with amines, amino acids, and a biotin derivative targeted for monoclonal antibody−avidin conjugates.

Scheme 1





Results and Discussion

Synthesis and Characterization of Organoimido Succinimidyl Esters 2−4. Iminophosphoranes are known to react with rhenium(V) oxo complexes to form arylimidorhenium(V) complexes and triphenylphosphine oxide.[9] The bis-triphenylphosphine organoimidorhenium *N*-succinimidyl ester complex $Cl_3(PPh_3)_2$-Re=N-$C_6H_4CO_2N(COCH_2)_2$ (**2**) was prepared in 91% yield by heating the rhenium(V) oxo complex $ReOCl_3(PPh_3)_2$ in benzene for 1 h with the iminophosphorane derived from *N*-succinimidyl-4-azidobenzoate (Scheme 1).[10] No precautions to dry the solvent or exclude air were required. The complex exhibits a single $^{31}P\{^1H\}$ NMR signal at δ −23.7 for the equivalent *trans* triphenylphosphine ligands. The complex was fully characterized by ^1H and ^{13}C NMR and elemental analysis. The FT-IR absorbances of the ester and imide carbonyl groups occur at 1770 and 1743 cm^{-1}, respectively. The complex exhibits a characteristic UV−vis absorbance at λ = 336 nm, ϵ = 14 030 in CH_2Cl_2 and is easily

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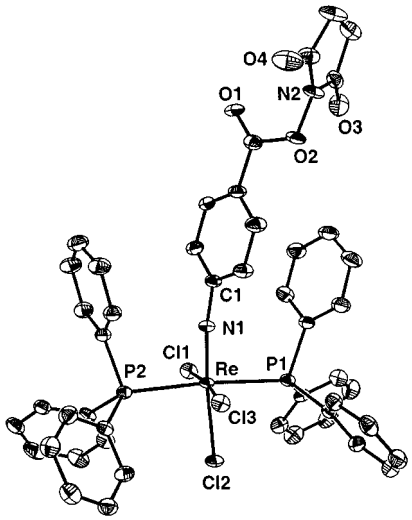

Figure 1. ORTEP drawing (50% probability ellipsoids) of $Cl_3(PPh_3)_2Re{=}N\text{-}C_6H_4CO_2N(COCH_2)_2{\cdot}(CH_2Cl_2)_{1.43}\text{-}(EtOH)_{0.57}$. Hydrogen atoms and disordered lattice molecules are omitted.

Table 1. Summary of Crystallographic Data

chemical formula	$C_{49.57}H_{44.28}Cl_{5.86}N_2O_{4.57}P_2Re$
temp (K)	203
space group	$P\bar{1}$ (No. 2)
cryst dimens (mm)	0.18 × 0.23 × 0.68
a, Å	12.703(3)
b, Å	14.250(3)
c, Å	14.930(3)
α, deg	100.04(3)
β, deg	105.40(3)
γ, deg	101.23(3)
cryst syst	triclinic
Z, volume (Å^3)	2, 1197.0
density (calcd) (g/cm^3)	1.60
abs coeff (mm^{-1})	2.88
transmission factors	0.592, 0.719
θ range for data collection (deg)	2.0−25.0
limiting indices	$-15 \le h \le 0$, $-16 \le k \le 16$, $-17 \le l \le 17$
no. of reflns collected	8965
no. of indepdt reflns, R_{int}	8537, 0.029
R^a	0.034

^{a} $R = (\Sigma||F_{obs} - F_{calc}||)/(\Sigma F_{obs})$.

Table 2. Selected Bond Lengths (Å) and Angles (deg) for 2

bond distances		bond angles	
Re−N1	1.721(4)	Re−N−C1	171.4(4)
Re−Cl1	2.440(1)	P1−Re−P2	175.3(1)
Re−Cl2	2.411(1)	Cl2−Re−Cl3	85.4(1)
Re−P1	2.524(2)	Cl1−Re−N	93.9(1)
Re−P2	2.518(2)	Cl1−Re−P1	89.7(1)
N1−C1	1.380(6)	Cl1−Re−P2	90.0(1)
O1−C7	1.211(6)	Cl1−Re−Cl2	90.4(1)

distinguished from the oxo complex $ReOCl_3(PPh_3)_2$, which absorbs at 272 nm.

The structure of the complex **2** (Figure 1) consists of an octahedral arrangement of *mer-cis*-oriented chloride ligands, *trans*-triphenylphosphine ligands, and the imido ligand. This ligand arrangement around the rhenium is similar to that of previously reported phenylimido complexes and is consistent with spectroscopic data for the complex in solution. A summary of crystallographic data is reported in Table 1. Selected bond lengths and angles are reported in Table 2. The Re−N bond length of 1.721(4) Å and the nearly linear Re−N−C1 organoimido bond angle of 171.4(4)° are typical of multiple bonded rhenium(V) monoimido complexes (1.69−1.75 Å, 156−180°).[11] The Re−Cl and Re−P distances are similar to those reported for the closely related complex $[Re(NPh)Cl_3(PPh_3)_2]$.[12] The *N*-succinimidyl ester carbonyl group of **2** is situated remotely from the coordination environment of the metal and is not perturbed by it.

The monomeric dithiocarbamate complex $Cl[Et_2NCS_2]_2Re{=}N\text{-}C_6H_4CO_2N(COCH_2)_2$ (**3**) was prepared in 84% yield by heating a solution of **2** with tetraethylthiuramdisulfide in acetone for 1 h (Scheme 1).[13] The ^{1}H NMR spectra of **3** in $CDCl_3$ at 22 °C shows a single triplet for the four methyl groups and a multiplet for the inequivalent CH_2 groups due to slow rotation about the C−N bond of the dithiocarbamate ligands. The ethyl groups in **3** give rise to two ^{13}C NMR peaks at *δ* 12.42 and 45.16. The FT-IR spectra show strong absorbances at 1531 and 997 cm^{-1} associated with the C−N and C−S bonds of the dithiocarbamate ligand. The absorbances for the ester and imide carbonyls of **3** appeared at 1769 and 1741 cm^{-1} and are very close to the corresponding carbonyl groups of complex **2**. Complex **3** exhibits a UV−vis absorbance in CH_2Cl_2 at 418 nm, $\epsilon = 4710$ that is easily distinguished from the oxo complex $Cl[Et_2NCS_2]_2\text{-}Re{=}O$, which absorbs at 344 nm.

The tetrakis(dithiocarbamate) *μ*-oxo-dirhenium complex $O[(Et_2NCS_2)_2Re{=}N\text{-}NC_6H_4CO_2N(COCH_2)_2]_2$ (**4**) was prepared in 73% yield by treating **3** with sodium carbonate in 0.1% v/v aqueous acetone and heating for 1 h (Scheme 1).[13] The ^{1}H NMR spectra of **4** in $CDCl_3$ at 22 °C shows a single triplet for the four methyl groups and a multiplet for the CH_2 groups of the dithiocarbamate ligand. The FT-IR spectra of **4** shows strong absorbances of the dithiocarbamate ligand at 1500 and 1072 cm^{-1} and also an absorbance at 684 cm^{-1} due to the bridging *μ*-oxo Re−O−Re group. The absorbance of the ester carbonyl in **4** is shifted to 1780 cm^{-1}, an increase of +10 cm^{-1} compared with complexes **2** and **3**. This shift indicates the apparently greater electron-withdrawing effect of the bridging oxo group in comparison with the chloride ligand, which influences the remote conjugated carbonyl through the phenylimido group. Complex **4** showed a UV−vis absorbance at 444 nm in CH_2Cl_2; however this absorbance exhibited a nonlinear dependence on concentration. Similar deviations from the Beer−Lambert law have been observed in the electronic spectra of related oxo-bridged organoimido molybdenum dimers and were attributed to an equilibrium disproportionation reaction.[14] The corresponding oxo dimer $O[(Et_2NCS_2)_2Re{=}O]_2$ absorbs at 388 nm in CH_2Cl_2 and is easily distinguished from the organoimido complex **4**.

Stability Studies of Organoimido Succinimidyl Esters 2−4. The characteristic UV−vis absorbances of the organoimido complexes were useful for monitoring the stability of the organoimido bond toward hydrolysis in solution. For the developmental stage of this project,

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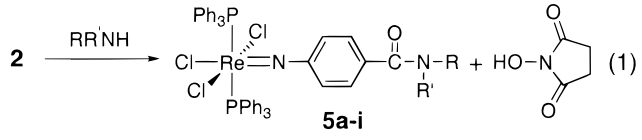
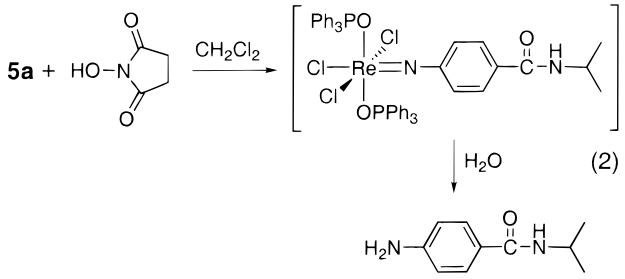
the stability of the complexes over the course of a 3 h time period was taken as representative of the necessary time for preparing, administering, and imaging a potential organoimido radiopharmaceutical. Solutions of all three of the organoimido complexes in CH_2Cl_2 or $CDCl_3$ were stable for several days at room temperature, exhibiting no change in either their absorbance spectra or their ^1H NMR. The complex **2** was not soluble in water alone, but dilute solutions (10^{-5} M) in 10% DMF/H_2O were prepared by first dissolving the complex in DMF and then diluting with H_2O. The complex **2** decomposed slowly in the aqueous media, exhibiting 30% hydrolysis after 3 h. The simple oxo complex $ReOCl_3(PPh_3)_2$ resulting from hydrolysis of the organoimido bond was observed by UV−vis, and corresponding amounts of the aniline $H_2NC_6H_4CO_2N(COCH_2)_2$ were isolated. Hydrolysis of the succinimide ester group was not observed during the 3 h time period. The monomeric chloro dithiocarbamate complex **3** rapidly dimerized in 10% DMF/H_2O to form **4**. This reaction is similar to the preparative dimerization that is carried out in aqueous acetone in the presence of base and precludes the formation of monomeric complexes from **3** in the presence of H_2O.[13] The μ-oxo dimer complex **4** was very stable in the aqueous DMF and exhibited no hydrolysis of the organoimido bond after 3 h, as evidenced by NMR and UV−vis.

Reactivity of *N*-Succinimidyl Ester 2 with Amines. The amine coupling reactions of **2** were initially conducted with isopropylamine using CH_2Cl_2 as solvent (eq 1). In this reaction the nucleophilic amine



undergoes acylation with the succinimidyl ester complex **2** to produce the amide product **5a** and 1 equiv of *N*-hydroxysuccinimide $HON(COCH_2)_2$. Because the ultimate goal was to develop practical amine labeling agents, no efforts were taken to dry solvents and reagents or to exclude air from the reactions. The amide product **5a** was isolated by precipitation with hexanes after concentrating the solvent. The complex **5a** was characterized by ^1H and ^{13}C NMR and elemental analysis. The FT-IR of **5a** shows the absorbance of the amide C═O group at 1639 cm^{-1}. The isolated yields of product **5a** from repeated experiments in CH_2Cl_2 were consistently below 30% and were accompanied by large amounts of triphenylphosphine oxide ($OPPh_3$), succinimide $HN(COCH_2)_2$, and the hydrolyzed amide $H_2NC_6H_4CONHCH(CH_3)_2$. The yields of product **5a** were not improved when this reaction was repeated using anhydrous CH_2Cl_2 under an atmosphere of argon. The isolated product **5a** was found to be stable in the presence of excess isopropylamine in CH_2Cl_2 solution for at least 6 h.

A control experiment was performed to evaluate the stability of **5a** in the presence of $HON(COCH_2)_2$, the reaction byproduct of amide formation. A 10^{-2} M solution of the amide complex **5a** in CH_2Cl_2 was treated with 2 equiv of $HON(COCH_2)_2$, and the UV−vis spectrum was monitored during the course of the reaction. The absorbance due to the coordinated PPh_3 ligands at 264 nm decreased in intensity and was completely replaced by the appearance of $OPPh_3$ after 1 h. The absorbance at 342 nm shifted slightly to 362 nm, suggesting the possible existence of a phosphine oxide complex with an intact organoimido bond. The addition of water eliminated the absorbance at 362 nm and caused decomposition of the complex along with hydrolysis of the organoimido group to produce the aniline derivative $H_2NC_6H_4CONHCH(CH_3)_2$, which was isolated from the reaction mixture in 68% yield after silica gel chromatography (eq 2). Attempts to isolate the putative phos-



phine oxide complex from these reactions and preparations carried out with exclusion of O_2 and H_2O were unsuccessful. The PPh_3 ligands in complex **5a** were not displaced by the addition of excess $OPPh_3$. The low amide coupling yields of **5a** with isopropylamine in CH_2Cl_2 can therefore be attributed to oxidation of the coordinated phosphine ligands by $HON(COCH_2)_2$, which is released after each coupling event, followed by hydrolysis of the imido bond, which occurs faster in complexes containing phosphine oxide ligands. The oxygen atom transfer chemistry to the coordinated PPh_3 from *N*-hydroxysuccinimide in CH_2Cl_2 was unexpected and to the best of our knowledge unprecedented in the literature, although various other *N*-oxides are recognized as thermodynamically favorable oxidants toward oxidation of PPh_3.[15]

The yield of the coupling reaction was significantly improved by changing the solvent to DMF, and complex **2** reacted with a series of amines to produce the corresponding amide complexes **5a**−**i**, Table 3. In a typical reaction, complex **2** was treated with 10 equiv of the amine in DMF (0.025 M) at 25 °C for 10 min, followed by the addition of water to precipitate the amide products. Two factors contributed to the dramatic success of this procedure: the enhanced rate of amide formation in DMF and the ability to precipitate the products with H_2O, which concentrated the $HON(COCH_2)_2$ in the aqueous phase, thereby preventing it from oxidizing bound PPh_3 ligands of the metal products. The yields of the organoimido amide products from primary and secondary amines using this procedure varied from 67% to 78%. Complexes **5a**, **5d**, **5e**, and **5f** were recrystallized from CH_2Cl_2, and the solids retained some CH_2Cl_2 solvent, which was not removed by drying in vacuo and was evident in the NMR spectra and elemental analyses of these compounds. The ethyl ester hydrochloride salts of alanine and cysteine were coupled under similar conditions in the presence of added triethylamine, producing amides **5g**,**h** in 67% and 74% yields, respectively. The success of the coupling reaction

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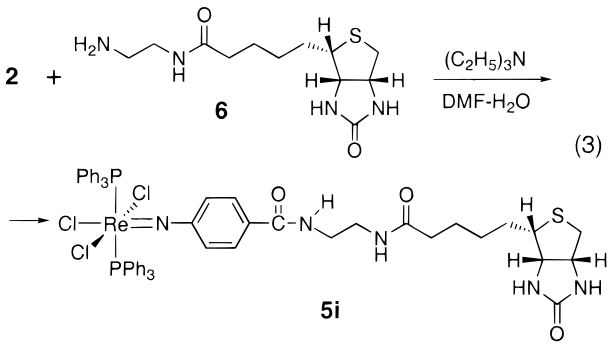
Table 3. Coupling of 1° and 2° Amines with 2[a]

entry	amine	product-amide	yield (%)
1	isopropylamine	**5a**: R′ = H R = −CH(CH$_3$)$_2$	70
2	2-amino-3-methylbutane	**5b**: R′ = H R = −CH(CH$_3$)CH(CH$_3$)$_2$	69
3	phenethylamine	**5c**: R′ = H R = −CH$_2$CH$_2$−C$_6$H$_5$	67
4	benzylamine	**5d**: R′ = H R = −CH$_2$−C$_6$H$_5$	72
5	pyrrolidine	**5e**: R = R′ = N(CH$_2$CH$_2$)$_2$	70
6	morpholine	**5f**: R′ = R = N(CH$_2$CH$_2$)$_2$O	78
7	alanine ethyl ester hydrochloride[b]	**5g**: R′ = H, R = −CH(CH$_3$)CO$_2$CH$_2$CH$_3$	67
8	cysteine ethyl ester hydrochloride[b]	**5h**: R′ = H, R = CH(CH$_2$SH)CO$_2$CH$_2$CH$_3$	74
9	**6**[b]	**5i**: R′ = H R = −(CH$_2$)$_2$NHC(O)biotin	49

[a] Reactions were carried out in DMF, and the product was precipitated with water. [b] Triethylamine (2 mmol) was added in the reaction mixture.

in the presence of the free sulfhydryl group of cysteine is particularly notable considering the strong potential for ligation of this group. Solutions of the cysteine complex **5h** did exhibit slow decomposition after several hours at ambient temperature, which presumably could be initiated by intermolecular ligand substitution reactions involving the sulfhydryl group.

There has been a great deal of interest in preparing labeled biotin derivatives for use in radioimmunodetection and radioimmunotherapy.[16] In the pretargeting approach, monoclonal antibody−avidin conjugates are allowed to localize at their target site, followed by treatment with a radiolabeled biotin derivitive, which is then selectively accumulated due to the high binding affinity of avidin for biotin. The ethylenediamine derivative of biotin **6** was prepared following the literature procedure.[17] The coupling reaction of **2** with **6** was performed in DMF as described above and afforded the biotin−amide derivative **5i** in 49% isolated yield (eq 3). The amide coupling proceeded to completion; however



the lower isolated yield in this case can be attributed to the solubility characteristics of the biotin moiety in **5i**, which adversely affected the precipitation of the complex. The complex was characterized by $^{31}P\{^1H\}$, ^1H, and ^{13}C NMR.

Reactivity of Dithiocarbamate Complexes 3 and 4. Recognizing the problems associated with oxidation of the phosphine ligands by *N*-hydroxysuccinimide, we decided to investigate analogous organoimido complexes containing nonoxidizable ligands. Organoimidorhenium(V) dithiocarbamate complexes are well-known and can be prepared directly from the phosphine complexes.[9b,13,18] The replacement of chloride ligands is an additional important structural difference in these types of complexes. Solutions of complexes **3** and **4** in CH_2Cl_2 and $CDCl_3$ were monitored by UV−vis and ^1H NMR, respectively, and found to be stable in the presence of excess *N*-hydroxysuccinimide for at least 3 days at ambient temperature. The dimerization of the chloro complex **3** in the presence of H_2O was described previously, and reactions of **3** with excess isopropylamine in CH_2Cl_2 containing trace amounts of water resulted in the formation of the bridging μ-oxo dimer O[ReO(S$_2$CNEt$_2$)$_2$]$_2$ and the hydrolyzed aniline derivative $H_2NC_6H_4CONHCH(CH_3)_2$. The dimeric succinimide ester complex **4** reacted with isopropylamine in CH_2Cl_2 with traces of H_2O to give only low yields of the desired amide product and was also accompanied by larger amounts of the hydrolysis product O[ReO(S$_2$CNEt$_2$)$_2$]$_2$. When the reaction of **4** with isopropylamine was performed in 10% DMF/H_2O, none of the desired bis-organoimido μ-oxo dimer O[Re═N-C$_6$H$_4$CONHCH(CH$_3$)$_2$(S$_2$CNEt$_2$)$_2$]$_2$ was isolated; only the hydrolyzed aniline and μ-oxo dimer O[ReO(S$_2$CNEt$_2$)$_2$]$_2$ were obtained. These results contrast with the general stability of complex **4** in aqueous DMF alone, but may simply reflect the enhanced nuleophilicity of water in the presence of an alkylamine base. Thus, while the organoimido dithiocarbamate complexes were unaffected by *N*-hydroxysuccinimide, these complexes were subject to the more severe problem of hydrolysis of the imido bond in the presence of amines.

Conclusions

A series of organoimido complexes possessing remotely functionalized succinimidyl ester groups were synthesized. The organoimidorhenium(V) *N*-hydroxysuccinimidyl ester phosphine complex **2** is an effective labeling agent for alkylamines when the reactions are carried out in aqueous DMF solution. A series of primary and secondary amines, amino acids, and a biotin−ethylenediamine derivative were successfully coupled with **2** to give the corresponding amides in good yields.

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These results demonstrate the stability of the organoimido linkage against competing hydrolysis to the oxo and in the presence of more basic alkylamines. When CH_2Cl_2 solvent was used, the amide formation was slower, and oxidation of the PPh_3 ligands by the released *N*-hydroxysuccinimide caused decompostion of the organoimido complexes. The dithiocarbamate complexes **3** and **4** were unaffected by *N*-hydroxysuccinimide, but the organoimido groups were not stable under the reaction conditions with alkylamines and hydrolysis to the oxo complexes was observed. The problem of PPh_3 oxidation of **2** could potentially be avoided by preparing other activated carboxylic acid derivatives such as the pentachlorophenol or nitrophenol esters. The stability of the organoimido bond is dramatically affected by the nature of the ancillary ligands, and further efforts will attempt to develop systems with enhanced stability and water solubility.

Experimental Section

General Procedures. Reagents were purchased from Aldrich or Acros and used as received. Trichlorooxobis(triphenylphosphine)rhenium(V) was prepared according to the literature procedure.[19] ^{1}H NMR and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, using $CDCl_3$ as solvent and internally referenced to TMS. $^{31}P\{^1H\}$ NMR spectra were obtained at 161.9 MHz, referenced to an internal capillary containing 85% $H_3PO_{4(aq)}$ ($\delta = 0$). IR spectra were recorded as KBr pellets using a Perkin-Elmer 1720 X FT-IR spectrometer. UV−vis spectra were recorded using a Hewlett-Packard 8452A diode array spectrophotometer. Elemental analyses were performed by Desert Analytics, Tucson, AZ.

Synthesis of $Cl_3(PPh_3)_2Re{=}N\text{-}C_6H_4CO_2N(COCH_2)_2$ (2). Triphenylphosphine (1.57 g, 6 mmol) was added to a solution of $N_3C_6H_4CO_2N(COCH_2)_2$ (780 mg, 3.0 mmol) in benzene (200 mL) and stirred for 20 min at 25 °C, and trichlorooxobis(triphenylphosphine)rhenium(V) (2.50 g, 3.0 mmol) was then added and the mixture heated to reflux for 1 h. The volatiles were removed in vacuo, and the product was recrystallized from dichloromethane by the addition of hexanes, filtered, and washed with Et_2O and hexanes to give a green solid, **2** (2.865 g, 91% yield): UV−vis (CH_2Cl_2) $\lambda = 234, 266, 298$ ($\epsilon = 16\,400$), 336 nm ($\epsilon = 14\,030$); FT-IR 1770, 1743, 1197, 745, 694, 521 cm^{-1}; ^{1}H NMR δ 7.88−7.72 (m, 12H), 7.52 (d, $J = 8.6$ Hz, 2H), 7.35−7.20 (m, 18H), 6.88 (d, $J = 8.6$ Hz, 2H), 2.91 (s, 4H); ^{13}C NMR δ 169.36, 160.49, 135.21, 132.22, 131.73, 131.17, 130.78, 128.22, 123.20, 121.31, 26.07; $^{31}P\{^1H\}$ NMR δ −23.66 (s). Anal. Calcd for $C_{47}H_{38}Cl_3N_2O_4P_2Re$: C, 53.80; H, 3.65; N, 2.67. Found: C, 53.73; H, 3.65 N, 2.66.

Synthesis of $Cl[(Et)_2NCS_2]_2Re{=}N\text{-}C_6H_4CO_2N(COCH_2)_2$ (3). A mixture of **2** (300 mg, 0.28 mmol) and tetraethylthiuramdisulfide (170 mg, 0.57 mmol) was heated at reflux in dry acetone (20 mL) under argon for 1 h, during which time the solution became dark green. The volume was reduced to 5 mL, and the flask was cooled in an ice bath to crystallize the complex. The complex was filtered and washed with cold acetone and Et_2O to give **3** (150 mg, 84% yield): UV−vis (CH_2Cl_2): $\lambda = 234, 272, 296$ ($\epsilon = 24\,045$), 418 nm ($\epsilon = 4710$); FT-IR 1769, 1741, 1531, 1073, 997 cm^{-1}; ^{1}H NMR δ 7.99 (d, $J = 8.6$ Hz, 2H), 7.54 (d, $J = 8.6$ Hz, 2H) 3.95−3.65 (m, 8H), 2.89 (s, 4H), 1.38 (t, $J = 7.1$ Hz, 12H); ^{13}C NMR δ 239.88, 168.95, 161.12, 131.51, 123.81, 122.79, 45.16, 25.50, 12.42. Anal. Calcd for $C_{21}H_{28}ClN_4O_4S_4Re$: C, 33.61; H, 3.76; N, 7.47. Found: C, 33.37; H, 3.74; N, 7.41.

Synthesis of $O[((Et)_2NCS_2-)_2Re{=}N\text{-}C_6H_4CO_2N(COCH_2)_2]_2$ (4). To a solution of complex **3** (100 mg, 0.13 mmol) in 0.1% v/v aqueous acetone (20 mL) was added sodium carbonate (400 mg), and the mixture was heated at reflux for 2 h. The reaction mixture was filtered and concentrated in vacuo, and the crude product was isolated by addition of hexanes to a dichloromethane solution and purified by recrystallization from hexanes/CH_2Cl_2 to give the product **4** (70 mg, 73% yield): UV−vis (CH_2Cl_2) $\lambda = 244, 268, 348, 444$ nm; FT-IR 1780, 1744, 1500, 1072, 684 cm^{-1}; ^{1}H NMR δ 7.88 (d, $J = 8.7$ Hz, 4H), 7.28 (d, $J = 8.2$ Hz, 4H), 3.95−3.55 (m, 16H), 2.87 (s, 8H), 1.37 (t, $J = 7.0$ Hz, 24H); ^{13}C NMR δ 239.47, 169.27, 164.24, 130.99, 124.55, 118.70, 43.70, 25.53, 12.63.

Synthesis of $Cl_3(Ph_3P)_2Re{=}N\text{-}C_6H_4CONHCH(CH_3)_2$ (5a). Isopropylamine (50 μL, 1 mmol) was added to a solution of **2** (105 mg, 0.1 mmol) in DMF (4 mL) and stirred at 25 °C for 10 min. Water (36 mL) was added while stirring vigorously to precipitate the complex. The product was filtered, washed with water and hexanes, and then recrystallized from dichloromethane by adding hexanes to give the green solid **5a** (70 mg, 70% yield): UV−vis (CH_2Cl_2) $\lambda = 234, 264, 346$ nm ($\epsilon = 13000$); FT-IR 1639, 1525, 1435, 1093, 745, 694, 521 cm^{-1}; ^{1}H NMR δ 7.85−7.70 (m, 12H), 7.38−7.15 (m, 20H), 6.88 (d, $J = 8.4$ Hz, 2H), 5.76 (m, 1H), 4.23 (m, 1H), 1.26 (d, $J = 6.4$ Hz, 6H); ^{13}C NMR δ 163.62, 158.19, 135.33, 133.29, 132.17, 131.67, 130.70, 128.22, 121.76, 42.81, 23.13; $^{31}P\{^1H\}$ NMR δ −21.05 (s). Anal. Calcd for $C_{46}H_{42}Cl_3N_2OP_2Re{\cdot}0.5CH_2Cl_2$: C, 53.86; H, 4.15; N, 2.70. Found: C, 53.89; H, 4.09; N, 2.77.

Synthesis of $Cl_3(Ph_3P)_2Re{=}N\text{-}C_6H_4CONHCH(CH_3)CH(CH_3)_2$ (5b). The procedure described for the synthesis of **5a** was repeated using **2** (105 mg, 0.10 mmol) and 2-amino-3-methylbutane (87 mg, 1.00 mmol) to give the green solid **5b** (70 mg, 69% yield): UV−vis (CH_2Cl_2) $\lambda = 234, 264, 346$ nm ($\epsilon = 11\,437$); FT-IR 1655, 1536, 1435, 1093, 745, 694, 521 cm^{-1}; ^{1}H NMR δ 7.88−7.68 (m, 12H), 7.40−7.10 (m, 20H), 6.88 (d, $J = 7.4$ Hz, 2H), 5.75 (m, 1H), 4.02 (m, 1H), 1.80 (m, 1H), 1.17 (d, $J = 6.6$ Hz, 3H), 0.95 (d, $J = 6.0$ Hz, 6H); ^{13}C NMR δ 165.22, 157.61, 134.73, 131.51, 131.09, 130.09, 127.59, 127.11, 121.20, 50.71, 32.86, 18.51, 17.36; $^{31}P\{^1H\}$ NMR δ −19.46.

Synthesis of $Cl_3(Ph_3P)_2Re{=}N\text{-}C_6H_4CONH(CH_2)_2Ph$ (5c). The procedure described for the synthesis of **5a** was repeated using **2** (50 mg, 0.05 mmol) and phenethylamine (50 μL, 0.50 mmol) to give the green complex **5c** (35 mg, 67%): UV−vis (CH_2Cl_2) $\lambda = 232, 264, 344$ nm ($\epsilon = 10\,598$); FT-IR 1665, 1541, 1093, 747, 694, 521 cm^{-1}; ^{1}H NMR δ 7.90−7.70 (m, 12H), 7.45−7.15 (m, 23H), 7.08 (d, $J = 8.4$ Hz, 2H), 6.82 (d, $J = 8.4$ Hz, 2H), 5.96 (m, 1H), 3.67 (q, $J = 6.7$ Hz, 2H), 2.92 (t, $J = 6.7$ Hz, 2H); ^{13}C NMR δ 166.48, 158.10, 139.12, 135.30, 132.08, 131.69, 131.15, 130.65, 129.23, 128.21, 127.87, 127.19, 121.77, 41.75, 35.87; $^{31}P\{^1H\}$ NMR δ −19.83 (s).

Synthesis of $Cl_3(Ph_3P)_2Re{=}N\text{-}C_6H_4CONHCH_2Ph$ (5d). The procedure described for the synthesis of **5a** was repeated using **2** (105 mg, 0.1 mmol) and benzylamine (110 μL, 1 mmol), and the crude product was recrystallized by slow diffusion of ethanol into a dichloromethane solution to give the green complex **5d** (75 mg, 72% yield): UV−vis (CH_2Cl_2) $\lambda = 234, 264, 344$ nm ($\epsilon = 13\,398$); FT-IR 1656, 1093, 745, 694, 521 cm^{-1}; ^{1}H NMR δ 7.82−7.73 (m, 12H), 7.40−7.30 (m, 5H), 7.26−7.17 (m, 20H), 6.86 (d, $J = 8.4$ Hz, 2H), 6.35 (t, $J = 5.2$ Hz, 1H), 4.58 (d, $J = 5.2$ Hz, 2H); ^{13}C NMR δ 166.30, 158.27, 138.19, 135.20, 133.97, 132.66, 132.06, 131.64, 130.63, 129.31, 128.56, 120.17, 121.75, 44.71; $^{31}P\{^1H\}$ NMR δ −21.29 (s). Anal. Calcd for $C_{50}H_{42}Cl_3N_2O_2P_2Re\text{-}0.25CH_2Cl_2$: C, 56.74; H, 3.98. Found: C, 56.92; H, 3.60.

Synthesis of $Cl_3(Ph_3P)_2Re{=}N\text{-}C_6H_4CON(CH_2)_4$ (5e). The procedure described for the synthesis of **5a** was repeated using **2** (50 mg, 0.05 mmol) and pyrrolidine (50 μL, 0.50 mmol), and the crude product was recrystallized by slow diffusion of ethanol into a dichloromethane solution to give the green complex **5e** (35 mg, 70% yield) and recrystallized from dichloromethane and ethanol: UV−vis (CH_2Cl_2) $\lambda = 232, 264, 344$ nm ($\epsilon = 10\,486$); FT-IR 1628, 1092, 745, 694, 521 cm^{-1}; ^{1}H NMR δ 7.85−7.65 (m, 12H), 7.30−7.15 (m, 18H), 6.93 (d, $J =$

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8.0 Hz, 2H), 6.86 (d, J = 8.0 Hz, 2H), 3.58 (t, J = 6.4 Hz, 2H), 3.22 (t, J = 6.4 Hz, 2H), 2.05−1.82 (m, 4H); ^{13}C NMR δ 168.65, 156.85, 135.31, 132.16, 131.66, 131.20, 130.60, 128.14, 121.64, 49.82, 46.73, 26.81, 24.79; ^{31}P{^{1}H} NMR δ −21.00 (s). Anal. Calcd for $C_{47}H_{42}Cl_3N_2OP_2Re\cdot0.5CH_2Cl_2$: C, 54.39; H, 4.10; N, 2.67. Found: C, 54.55; H, 4.13; N, 2.66.

Synthesis of $Cl_3(Ph_3P)_2Re{=}N\text{-}C_6H_4CON(CH_2CH_2)_2O$ (5f). The procedure described for the synthesis of **5a** was repeated using **2** (105 mg, 0.10 mmol) and morpholine (88 μL, 1.00 mmol), and the precipitated product was recrystallized by slow diffusion of ethanol into a dichloromethane solution to give the green complex **5f** (80 mg, 78%): UV−vis (CH_2Cl_2) λ = 234, 264, 344 nm (ϵ = 13 922); FT-IR 1636, 1093, 746, 694, 521 cm^{-1}; ^{1}H NMR δ 7.85−7.65 (m, 12H), 7.30−7.15 (m, 18H), 6.88 (d, J = 8.0 Hz, 2H), 6.81 (d, J = 8.0 Hz, 2H), 3.99 (m, 2H), 3.80−3.50 (m, 4H), 3.25 (m, 2H); ^{13}C NMR δ 169.39, 156.93, 135.33, 132.22, 131.73, 131.17, 130.62, 128.16, 121.85, 61.12, 48.64; ^{31}P{^{1}H} NMR δ −21.36 (s). Anal. Calcd for $C_{47}H_{42}Cl_3N_2O_2P_2Re\cdot0.5CH_2Cl_2$: C, 53.57; H, 4.04; N, 2.63. Found: C, 53.16; H, 3.92; N, 2.64.

Synthesis of $Cl_3(Ph_3P)_2Re{=}N\text{-}C_6H_4CONHCH(CH_3)CO_2Et$ (5g). Triethylamine (300 μL, 2.00 mmol) was added to a solution of alanine ethyl ester hydrochloride (303 mg, 2.00 mmol) in DMF (4 mL), and the solution was stirred for 15 min. A solution of complex **2** (210 mg, 0.20 mmol) in DMF (4 mL) was then added, and the mixture was stirred for 10 min. Water (72 mL) was added, and the precipitated product **5g** was isolated by filtration and was subsequently recrystallized by addition of hexanes to a CH_2Cl_2 solution (140 mg, 67% yield): UV−vis (CH_2Cl_2) λ = 232, 264, 342 nm (ϵ = 12 000); FT-IR 1737, 1666, 1092, 750, 693, 521 cm^{-1}; ^{1}H NMR δ 7.85−7.68 (m, 12H), 7.35−7.15 (m, 20H), 6.87 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 7.2 Hz, 1H), 4.70 (m, 1H), 4.25 (q, J = 7.0 Hz, 2H), 1.51 (d, J = 6.8 Hz, 3H), 1.32 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 172.90, 165.28, 157.90, 134.70, 131.54, 131.11, 130.70, 130.09, 127.59, 121.19, 61.77, 48.63, 18.38, 14.01; ^{31}P{^{1}H} NMR δ -21.50 (s). Anal. Calcd for $C_{48}H_{44}Cl_3N_2OP_2Re$: C, 54.83; H, 4.22; N, 2.66. Found: C, 54.83; H, 4.18; N, 2.79.

Synthesis of $Cl_3(Ph_3P)_2Re{=}N\text{-}C_6H_4CONHCH(CH_2SH)\text{-}CO_2Et$ (5h). The procedure described for the synthesis of **5g** was repeated using the cysteine ethyl ester hydrochloride (370 mg, 2.00 mmol), DMF (3 mL), triethylamine (300 μL, 2.00 mmol), **2** (210 mg, 0.20 mmol), DMF (3 mL), and water (54 mL). The product was recrystallized from dichloromethane and hexanes to give the green complex **5h** (160 mg, 74% yield): UV−vis (CH_2Cl_2) λ = 234, 264, 336 nm (ϵ = 14 870); FT-IR 1737, 1665, 1093, 746, 694, 521 cm^{-1}; ^{1}H NMR δ 7.82−7.70 (m, 12H), 7.35−7.15 (m, 20H), 6.88 (d, J = 8.0 Hz, 2H), 4.99 (m, 1H), 4.35−4.25 (m, 3H), 3.20−3.05 (m, 2H), 1.34 (t, J = 7.6 Hz, 3H); ^{31}P{^{1}H} NMR δ −21.23 (s).

Synthesis of $Cl_3(Ph_3P)_2Re{=}N\text{-}C_6H_4CONH(CH_2)_2NH$−Biotin (5i). The procedure described for the synthesis of **5g** was repeated with **6** (108 mg, 0.38 mmol), DMF (6 mL), triethylamine (86 μL, 0.57 mmol), complex **2** (200 mg, 0.19 mmol), DMF (6 mL), and water (108 mL). The product was recrystallized from dichloromethane and hexanes to give the green complex **5i** (107 mg, 49%): UV−vis (CH_2Cl_2) λ = 232, 264, 342 nm (ϵ = 7045); FT-IR 1705, 1655, 1544, 1435, 1093, 747, 694, 521 cm^{-1}; ^{1}H NMR ($CDCl_3$+CD_3OD) δ 7.88−7.68 (m, 12H), 7.48−7.22 (m, 20H), 6.88 (d, J = 8.0 Hz, 2H), 4.55−4.40 (m, 1H), 4.35−4.22 (m, 1H), 3.58−3.32 (m, 4H), 3.20−2.65 (m, 3H), 2.23 (t, J = 8 Hz, 2H), 1.85−1.25 (m, 4H); ^{13}C NMR ($CDCl_3$+CD_3OD) δ 175.71, 167.42, 157.95, 135.06, 133.79, 131.87, 131.42, 130.57, 128.66, 128.07, 121.67, 62.25, 60.50, 55.73, 40.99, 40.58, 39.21, 35.87, 28.33, 25.66; ^{31}P{^{1}H} NMR δ −20.85 (s).

X-ray Structure Determination of $Cl_3(PPh_3)_2Re{=}N\text{-}C_6H_4CO_2N(COCH_2)_2\cdot(CH_2Cl_2)_{1.43}(EtOH)_{0.57}$. Complex **2** was crystallized by slow diffusion of ethanol into a CH_2Cl_2 solution of **2** at room temperature to give green, rod-shaped crystals of the complex $\mathbf{2}\cdot(CH_2Cl_2)_{1.43}\cdot(EtOH)_{0.57}$. A suitable crystal was suspended in viscous mineral oil, mounted on a glass fiber, and cooled to −70 °C. Data collection was performed by a Siemens R3m/V diffractometer operating in the θ−2θ scan mode with graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å) as previously described.[20] Intensities were corrected for Lorentz and polarization effects, and empirical absorption corrections were applied based on a set of ψ scans. The structure was solved by direct methods using Siemens' SHEXTL PLUS structure package. The unit cell and lack of systematic absences indicated a Laue symmetry of triclinic and the space group $P\bar{1}$. Two solvent molecules are included in the asymmetric unit, with one exhibiting complex disorder. This site refined adequately for 57% occupancy by EtOH and 43% occupancy by CH_2Cl_2, disordered over three positions. The structure was refined with full-matrix least-squares, and all non-hydrogen atoms in **2** and the ordered CH_2Cl_2 were refined anisotropically. The positions of the hydrogen atoms were calculated (C−H = 0.95 Å) and allowed to ride isotropically on their respective carbons atoms during refinement. Refinement of the data converged with a goodness-of-fit of 1.20 and final residuals (for 7463 data with $F > 4\sigma_F$) of R = 3.44% and R_w = 4.19%. Crystallographic data are presented in Table 1; selected bond distances and angles are given in Table 2.

Acknowledgment. J.B.A. thanks the USAMRC Breast Cancer Research Program DAMD17-97-1-7120 and ACS-PRF for financial support. M.V.V. and M.S.H. were supported by NIH-MBRS undergraduate fellowships.

Supporting Information Available: Complete tabulations of crystallographic data, bond lengths and angles, atomic coordinates, and thermal parameters, a completely labeled ball-and-stick diagram, and copies of ^{1}H, ^{13}C{^{1}H}, and ^{31}P{^{1}H} NMR spectra for complexes **4**, **5b**, **5c**, **5h**, and **5i**. This material is available free of charge via the Internet at http://pubs.acs.org.

OM990929W

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