Communications to the Editor

A Convenient Three-Component Synthesis of Substituted Cyclopentadienyl Tricarbonyl Rhenium Complexes

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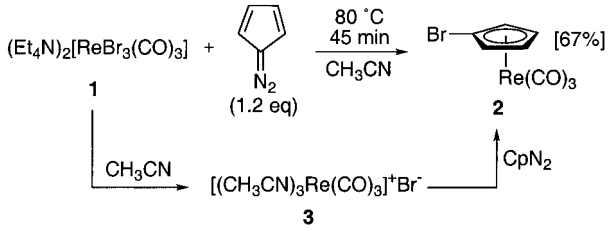
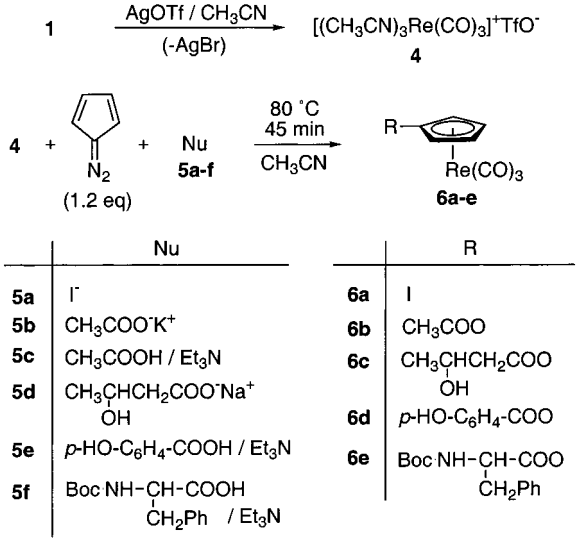
Radiolabeling biologically interesting molecules with ^{99m}Tc and ^{186}Re/^{188}Re is a subject of increasing interest because of the medical utility of these short-lived radionuclides.[1] ^{99m}Tc is the most widely used radionuclide for imaging,[2] while radiopharmaceuticals labeled with ^{186}Re and ^{188}Re have provided promising results in tumor radiotherapy.[3] There have been recent efforts devoted to the preparation of η^5-cyclopentadienyl-tricarbonyl-technetium $CpTc(CO)_3$ and rhenium $CpRe(CO)_3$ complexes,[4,5] since they present favorable structural and chemical features (small size, low polarity, high stability) and are very different from inorganic complexes of these metals.[6,7] However, up until now the preparation of these organometallic species has been cumbersome and has required rather harsh conditions.[4] As far as physical and chemical properties are concerned, technetium and rhenium are very similar.[8] Therefore, reactions involving the stable natural isotopes ^{185}Re and ^{187}Re can be reliably studied as models for the radioisotopes ^{186}Re/^{188}Re as well as for ^{99m}Tc.

Herein, we report a fast and versatile "one pot/three component assembly" reaction for the efficient synthesis of halo-, carbonyloxy-, and hydroxy-substituted $CpRe(CO)_3$ complexes, using diazocyclopentadiene (CpN_2) as the Cp precursor. Insertion reactions of CpN_2 with pentacarbonyl-rhenium halides [$ReX(CO)_5$] for the preparation of halogen-substituted $CpRe(CO)_3$ complexes have been reported.[9] However, the use of the pentacarbonyl precursor requires long reaction times (12−15 h in refluxing benzene for bromo- and iodo-$CpRe(CO)_3$), which are poorly suited for radiolabeling.

Scheme 1



Scheme 2



We have found that a different rhenium precursor, $(Et_4N)_2[ReBr_3(CO)_3]$ (**1**),[10] recently synthesized by a convenient low-pressure carbonylation/reduction of perrhenate,[11] once dissolved in acetonitrile, reacts much more readily with CpN_2, giving the bromo-substituted $CpRe(CO)_3$ **2**[9,12] in good yield after only 45 min at 80 °C (Scheme 1). The increased reactivity of this precursor is likely due to the known property of **1** to exchange all its three bromide anions with three molecules of a coordinating solvent like acetonitrile, to give the species **3**.[10] The dative solvent molecules are then readily displaced during coordination by a η^5-cyclopentadienyl (Cp) ligand (Scheme 1).

Although this transformation constitutes an important improvement of this precedented insertion reaction,[9] the substituent on the final complex so far was only a bromine, or potentially another halogen if the precursor was a different rhenium trihalide tricarbonyl species.[9] Therefore, we envisaged the possibility of replacing the bromide anion in the rhenium precursor **1** with a noncoordinating, nonnucleophilic counterion, such as a triflate (TfO^-), by treatment of a solution of **1** in acetonitrile with silver triflate (AgOTf), to give the species **4** (Scheme 2). This allowed us to study the introduction onto the Cp ring of "external" nucleophiles (**5a**−**f**), not already present in the rhenium precursor,

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(7) The large size and significant dipole moment associated with most inorganic Re and Tc complexes (generally tetradentate oxo−metal species) can change the properties of the ligand to which they are attached (or are part of) very significantly, thereby interfering with receptor binding affinity and cell membrane permeability. Some of these complexes also have limited stability under physiological conditions (see ref 6). These inconveniences may be avoided with cyclopentadienyl tricarbonyl metal systems.

(8) See: Boog, N. M.; Kaesz, H. D. Technetium and Rhenium. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, G. F. A., Abel, E. W., Eds.; Pergamon Press: Oxford, U.K., 1982; Vol. 4, pp 161−242.

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Table 1. Isolated Yield in the Reaction of **1** with CpN_2 (1.2 equiv) and Several Nucleophiles (2.0 equiv)[13]

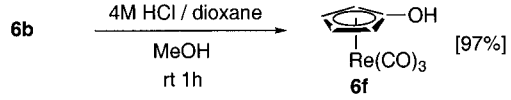
entry	nucleophile	isolated yield (%)[b]	product
1	**5a**	53	**6a**
2	**5b**	62	**6b**
3	**5c**[a]	69	**6b**
4	**5d**	59	**6c**
5	**5e**[a]	72	**6d**
6	**5f**[a]	60	**6e**

[a] Ratio carboxylic acid / Et_3N = 1:2. [b] Yields are referred to the initial rhenium precursor **1** (Schemes 1 and 2).

to give differently substituted $CpRe(CO)_3$ complexes (**6a**−**e**, Scheme 2). The most significant results are reported in Table 1. All yields are based on complexes isolated after purification by flash chromatography.[13]

It is worth noting that the yield range achieved (53−72%) is quite satisfactory, considering that this reaction simultaneously assembles three different components. Halide exchange of bromide with iodide worked well (entry 1), producing the iodo-substituted $CpRe(CO)_3$ **6a**,[9,14,15a] which had previously been shown to be an excellent substrate in the Stille coupling reaction with organo-tin reagents.[15] Even more interesting was the introduction of carboxylate substituents onto the Cp ring, because this constitutes a good method for directly binding the $CpRe(CO)_3$ portion to organic molecules. To the best of our knowledge, carbonyloxy-substituted $CpRe(CO)_3$ complexes have never been prepared before. As shown in Table 1, carboxylate salts proved to be excellent nucleophiles for this reaction (entry 2 and 4). Carboxylic acids could also be deprotonated in situ by triethylamine (Et_3N), as shown in entries 3, 5, and 6, without affecting the yields. Both aliphatic and aromatic carboxylic acids proved to be effective nucleophiles. Moreover, the reaction tolerates the presence of a free alcoholic (entry 4) or phenolic (entry 5) hydroxyl group, which does not compete with the carboxylate for nucleophilic substitution onto the Cp ring. Primary amine groups inhibit the reaction, but amide NH bonds are well-tolerated,

Scheme 3



as shown by the effective functionalization of the complex with an *N*-Boc protected amino acid (L-phenylalanine, entry 6). Preliminary experiments with thiols and acetylides, however, have so far not given satisfactory yields of the desired product, although further attempts are being made in order to extend this reaction to a wider variety of nucleophiles. Finally, hydrolysis of **6b** with a solution of HCl in dioxane and dry methanol gives **6f** in almost quantitative yields (Scheme 3), expanding the scope of this reaction to the preparation of hydroxy-substituted $CpRe(CO)_3$ complexes.

In summary, the reaction herein reported represents an efficient new approach to simultaneously assemble three different units (nucleophile, Cp, and Re precursors) to produce substituted $CpRe(CO)_3$ complexes in short reaction times and under mild conditions. To our knowledge, this method constitutes the first synthesis of R−COO−$CpRe(CO)_3$ and HO−$CpRe(CO)_3$ complexes, as well as an improved synthesis of halo−$CpRe(CO)_3$ complexes. We think that the results herein reported give useful indications of the possibility of attaching such complexes onto biologically interesting organic molecules, and thereby to produce new classes of rhenium- and technetium-labeled radiopharmaceuticals.[16]

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Supporting Information Available: Purification conditions and characterization data of compounds **6b**−**f** (5 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(13) Typical experimental procedure: 39 mg (0.050 mmol) of **1** were dissolved in anhydrous CH_3CN (1.5 mL) and treated with 40 mg (0.15 mmol) of AgOTf. AgBr was removed by filtration, and the supernatant was added to a solution containing CpN_2 (0.060 mmol) and the nucleophile (0.10 mmol) in CH_3CN (1 mL). If free carboxylic acids were used as the nucleophile, 0.20 mmol of triethylamine was also added. The mixture was heated at 80 °C for 45 min, then concentrated under vacuum. The crude reaction product was purified by flash chromatography. Characterization data and purification conditions of compounds **6b**−**f** are given in the Supporting Information.

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(16) We have successfully performed reactions to produce bromocyclopentadienyl tricarbonyl technetium from [^{99g}Tc]pertechnetate and chlorocyclopentadienyl tricarbonyl technetium from [^{99m}Tc]pertechnetate; yields comparable to those with perrhenate were obtained. This demonstrates that this reaction works well with technetium at both the macroscopic and tracer level.